Dissertation on

"COMPARISON BETWEEN BODE INDEX AND GOLD STAGING WITH RESPECT TO QUALITY OF LIFE AND C-REACTIVE PROTEIN LEVELS IN COPD PATIENTS"

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CERTIFICATE

This is to certify that the dissertation titled "**COMPARISON BETWEEN BODE INDEX AND GOLD STAGING WITH RESPECT TO QUALITY OF LIFE AND C-REACTIVE PROTEIN LEVELS IN COPD PATIENTS**" is the bonafide original work by **Dr.AISWARYA DHANAPALAN** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in APRIL 2016. The Period of study was from April 2015 to September 2015.

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DECLARATION

I, **Dr. AISWARYA DHANAPALAN** solemnly declare that dissertation titled "**COMPARISON BETWEEN BODE INDEX AND GOLD STAGING WITH RESPECT TO QUALITY OF LIFE AND C-REACTIVE PROTEIN LEVELS IN COPD PATIENTS**" is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2015 to September 2015 under the guidance and supervision of my unit chief **Prof.S.TITO**, Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – APRIL 2015.**

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CONTENTS

INTRODUCTION

INTRODUCTION

"Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent airflow limitation that is not fully reversible"[1]. COPD includes:

1) "Emphysema, defined as abnormalpermanent enlargement of distal airspaces, distal to terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis".
2) "Chronic bronchitis, clinically defined as the presence of chronic productive cough on most days for three months, in each of two consecutive years, in a patient in whom other cause of chronic cough has been excluded".

COPD has been implicated as a leading cause for worldwide mortality and morbidity. Exposure to tobacco smoking, outdoor, occupational and indoor air pollution is directly related to the prevalence of COPD. Spirometry is essential for diagnosis of COPD. A post bronchodilator Forced expiratory volume in 1 second (FEV_1) / Forced vital capacity(FVC) [FEV_1/FVC] less than 0.70 is essential for the diagnosis of COPD. COPD has now been found to be a systemic disease which affects lungs as well as other organ systems. Global Initiative for Chronic Lung Disease (GOLD) uses FEV_1 based staging system for assessing the severity of the disease. It has been found that FEV_1 based

staging system correlates poorly with symptoms of the patient, frequency of exacerbation, quality of life and intolerance to exercise. The multidimensional grading system, BODE index (body mass index, airflow obstruction , dyspnea and exercise capacity) has been shown to be a better predictor for risk of death among COPD patients than FEV_1. BODE index alsoprovides useful prognostic information.

Since COPD has been found to be associated with significant systemic inflammation, widespread research has been held in the field of biomarkers for COPD. Serum CRP levels have been found to be elevated even in stable COPD patients with no recent exacerbations. Basal CRP levels also helps in predicting overall mortality, mortality from cancer and cardiovascular diseases in patients with mild to moderate COPD.

For assessment of quality of life, various questionnaires have been developed which helps to establish the impact of the disease on patient's life.

In this study, it has been hypothesized that BODE index is a better predictor of health status of the patient, quality of life as well as systemic inflammation as compared to the FEV_1 based GOLD staging and aims to investigate the relationship of GOLD staging, BODE index with serum CRP levels, Quality of life, as well as prognostic factors in stable COPD patients.

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

- To investigate the relationship of severity of airflow limitation as assigned by GOLD staging, and BODE index with serum C- reactive protein levels, Quality of life as well as with prognostic factors like disease duration, annual exacerbation and hospital admission rates in stable COPD patients.

REVIEW

OF

LITERATURE

HISTORICAL REVIEW OF COPD

The earliest references for emphysema dates back to 1679 which include Bonet's description of voluminous lung; (Bonet 1679), Morgagni's account of 19 cases in 1769 in which the lungs were described as turgid which was due to air and Baille who illustrated the emphysematous lung (Baille1789; Bishop1959). Laennec also gave beautiful description of emphysema in his " Treatise of disease of chest" in which he emphasized that lungs were hyperinflated and did not empty well in emphysema (1821). He also gave a combined description of emphysema and chronic bronchitis.

Significant understanding of the chronic bronchitis component of COPD was obtained following the pioneering work of Badham who described chronic bronchitis and bronchiolitis as disabling disorders (Badham 1814). He had used the term "catarrh"to refer the chronic cough and mucous hypersecretion which were cardinal symptoms of chronic bronchitis.

Spirometer was introduced by John Hutchinson in 1846 which is integral for the diagnosis as well as management of COPD . But this instrument could only measure vital capacity and it was not before 1947, when Timed vital capacity was introduced as a measure of airflow by

Tiffeneau. This work laid foundation to the concept of airflow velocity index which was put forward by Gansler and this later became the basis for FEV_1 and FEV_1/FVC percent.

DEFINITION OF COPD

Even though several definitions exist for COPD, it would be unjustifiable to comment as one superior to other. The first definition came from the working group of American Thoracic Society (ATS) and the European Respiratory society (ERS). ATS 1995 had defined "COPD as a disease state characterized by the presence of airflow obstruction caused by chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper reactivity, and may be partially reversible."[2] ERS had defined COPD in 1995 as a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months."[3] But these definitions are not precise and may misdiagnose disease such as sarcoidos is cystic fibrosis, and bronchiectasis as COPD. More importantly44444 none of these definitions provide a clear cut difference between COPD and chronic asthma with airway remodeling. This is because, as mentioned by ATS,

some patients with COPD share some features of chronic ongoing asthma that make it difficult to differentiate the two.

Global initiative for Chronic Obstructive Lung Disease (GOLD) was launched in 2001, which put forward definition for COPD which was revised in 2006, 2011, 2015. GOLD 2015 describes “COPD as a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.”[1] Eventhough previous definition had stressed on terms emphysema and chronic bronchitis it had not been included in the current or earlier GOLD reports. In the previous definitions to make a diagnosis of COPD history of exposure to risk factors were not mandatory , but newer definitions clearly stresses on the history of exposure to risk factors to make a diagnosis.

Frequently the following components are considered while defining COPD:

1) Measure of airflow limitation and reversibility

Airflow limitation which is defined as a reduction in the velocity of expired air, incorporates a low FEV_1 and a low FEV_1 / FVC ratio post bronchodilator therapy. An FEV_1/FVC ratio less than 70% has been used to make a diagnosis of COPD[4,5]. “Airflow reversibility is defined as an

increase in FEV_1 by 200 ml and 12 from the baseline value in response to inhaled bronchodilators". The reversibility of airflow obstruction following inhalation of bronchodilator or to oral or inhaled corticosteroid had been frequently use to identify the patients who would benefit from bronchodilator therapy. The use of airflow reversibility neither increases the sensitivity or specificity of diagnosingCOPD[6] and the recent GOLD guidelines does not recommend the use of airflow reversibility for defining COPD.

2) Clinical features and overlap syndromes:

COPD includes chronic bronchitis and emphysema. Although significant advances in imaging fields helps in accurate diagnosis of emphysema, there exist significant variation in the physician diagnosis of both entities. As a result GOLD does not include these terms in definition of COPD.

Asthma is characterized by chronic airway inflammation and this leads to hyper responsiveness of airway which results in repeated attacks of wheezing, dyspnea, cough particularly at night or early hours of morning. These episodes have also been associated with widespread but variable airflow limitation which normalizes by itself or following treatment. Thus Asthma and COPD represents two separate diseases which have altogether different risk factors and pathogenesis, but the clinical features of the two may overlap which may lead to errors while

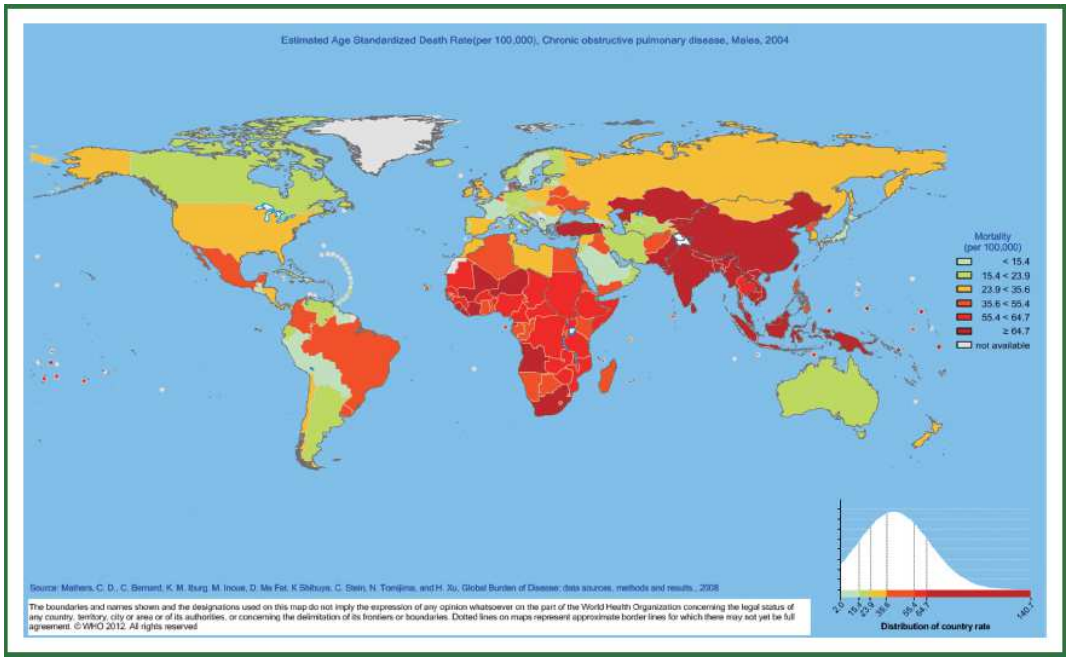
making a clinical diagnosis. But large population studies have found that a large proportion of the study candidates have been found to have more than one diagnosis (ie. Asthma and chronic bronchitis or emphysema[7,8] and this overlapping diagnosis are more common in elderly more than 50years and the probability increases with age.

EPIDEMIOLOGY

Global scenario

COPD represents one of the most prevalent diseases in the world. More than 210 million people have been affected globally. At present, COPD is the fourth most common cause of death worldwide, WHO has predicted that by 2030 it will be the third most common cause. Prevalence estimates of COPD depends on the criteria that is used for diagnosis. Until now, only a few studies have been able to provide a true estimate based on the standard spirometry definition. Even in United States studies were faced with major limitations which being firstly highly relying on the study participants and health care providers for proper recognition and diagnosis and secondly, they lack spirometry data to corroborate the evidence of airflow limitation. The study conducted by CDC in 2011 found that the prevalence was approximately 15 million in United States and it increased from 3.6 % among those less than 44 years to 11.6 % among those greater than 65 years. The overall prevalence of

COPD of GOLD stage II or higher was found to be 10.1 per cent and the prevalence in men accounted for 11.8 per cent and in women 8.5 per cent[9] was concluded from The Burden of Obstructive Lung Disease (BOLD) study from 12 sites involving 9425 subjects. The incidence of COPD varies greatly between countries, since they are reported in different units and over different lengths of time is difficult to do a comparison between the different studies that have been reported. In general incidence is greater in older people, particularly those aged 75 years and above. Studies done in Canada and USA have reported that trends in incidence were similar between men and women over time[10,11]. But in Australia it was found that incidence decreased among men and increased in women[12]. India and China accounts for a majority of COPD mortality and it has been found to be one among the highest in theworld. As per WHO Global Infobase it includes amongst both sexes more than 64.7 estimated age standardized death rate per 100,000 . From this data it can be inferred that, the annual number of cases in India to be approximately 556,000 (20%)[13]



"COPD mortality projection: Global Burden of Disease Data Updated 20th January 2011"

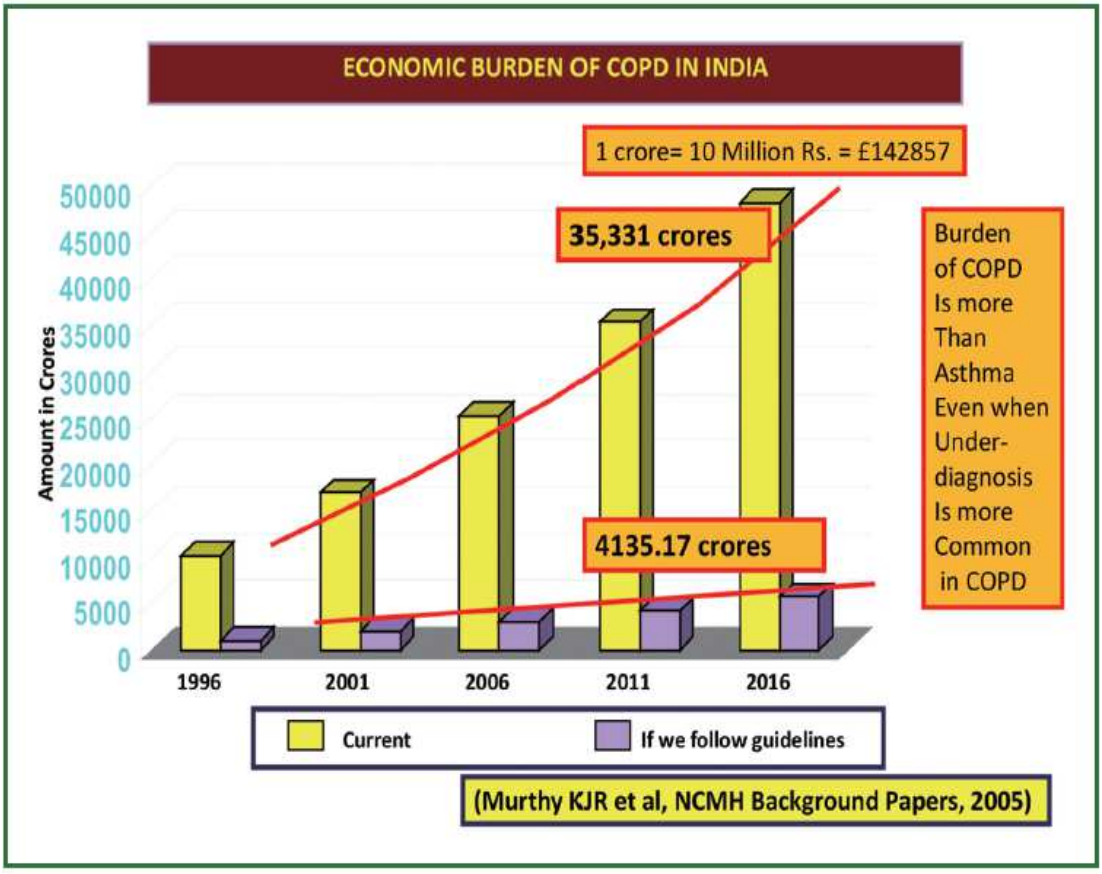
Indian Scenario

The earliest study to know the prevalence of COPD in India was carried in rural Delhi by out by Wig et al in 1964[14]. This study found a male preponderance of the disease with a prevalence of 3.36 % in males and 2.54% in females. In 1993, Jindal reported that the prevalence to be 6.2% in men and that in women as 3.9% in rural area, and in urban area it was 4.2 and 1.6 per cent, respectively[15]. All these study groups represented the population from north India and so the information regarding the prevalence from South India was meagre. Thiruvengadam et al in 1977 from Madras (south India) reported the prevalence of COPD of 1.9 per cent in males and 1.2 per cent in females[16] ·Ray et al in 1995[17]from south India found that the prevalence was 4.08 per cent in

males and 2.55 per cent in females. The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARECH) conducted a study around 2004-2006 involving a total of 85105 men, 84470 women from both urban and rural areas[18] This study showed that the overall prevalence of chronic bronchitis in adults >35 year was 3.49 per cent (ranging 1.1% in Mumbai to 10% in Thiruvananthapuram). The national burden of chronic bronchitis was estimated as 14.84 million based on this study. Smokers were found to have 3 times higher risk of developing COPD when compared to non-smokers and Bidi smokers were compared with their Cigarette smoking counterparts , the former was at a higher risk(8.2%) than latter (5.9%) .When the prevalence was compared with regard to cooking fuel exposure, it was 2% for those using LPG to about 5% among those using Kerosene and/or biomass fuels or firewood.

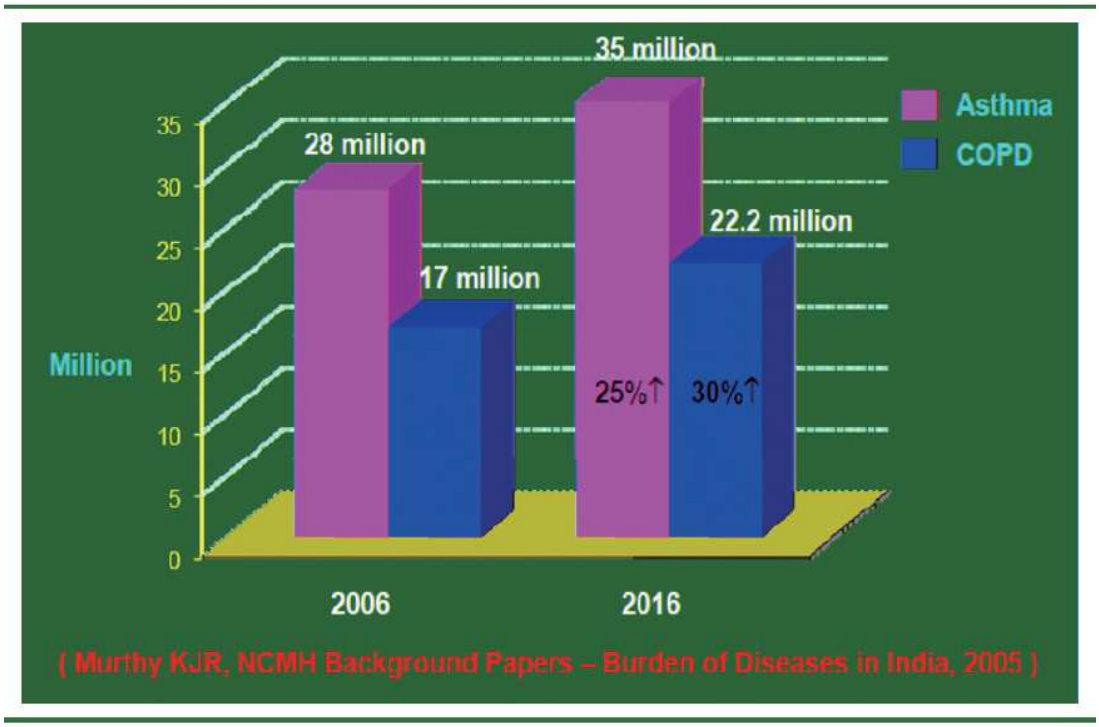
Table 1. Prevalence of COPD and its association with smoking in various population studies from India: Early studies 1964 to 1995.

	Population	COPD prevalence (%)		
		Men	Women	M:F Ratio
Wig [1964]	Rural Delhi	3.36	2.54	1.3
Sikand [1966]	Delhi	7.0	4.3	1.6
Viswanathan [1966]	Patna	2.12	1.33	1.6
Bhattacharya [1975]	Rural U.P	6.67	4.48	1.6
Radha [1977]	New Delhi	8.1	4.6	1.8
Thiruvengadam [1977]	Madras	1.9	1.2	1.6
Viswanathan [1977]	Delhi Rural	4.7	3.5	1.3
	Urban	8.0	4.3	1.9
Charan [1977]	Rural Punjab	2.28	1.63	1.4
Malik [1986]	N.India Rural	9.4	4.9	1.9
	Urban	3.7	1.6	2.3
Jindal [1993]	N.India Rural	6.2	3.9	1.6
	Urban	4.2	1.6	2.6
Ray [1995]	South India	4.08	2.55	1.6



"Estimated economic burden of COPD in India as per current practice"

According to the National Commission on Macroeconomics and Health (NCMH), which was set up in 2001 to study the burden of various diseases over the health care system of India, there were around 17 million COPD patients in 2006 and it is estimated to reach 22 million by around 2016[19]. The current economic burden of COPD is 35,000 crore Rs, and it is estimated to rise to a staggering 48,000 Crore Rs over next 5 years[19]



"Estimated number of cases of COPD in India in the current decade"

Causes of poor recgnition of COPD - burden and other pitfalls

1. Underdiagnosis and under assessment of COPD

- Nonspecific symptomatology
- Absence of awareness of a definite diagnosis – overlap of terminology
- Poor appreciation of symptom severity
- Non-availability or non-use of spirometry
- Slow progression

2. Lack of statistical information

- Inadequate epidemiological data
- Poor hospital records
- Poor recognition of mortality data
- Absence of burden assessment studies

3. Pitfalls of management

- Nonspecific management
- Absence of guideline directed treatment
- Inadequate preventive measures

"RISK FACTORS FOR DEVELOPMENT OF COPD"

Host based	Environmental
Genetic factors	Smoking
Asthma/ airway hyperreactivity	Occupational exposure
	Air pollution
	Childhood respiratory infections
	Low socioeconomic status

1. Genetic factors

- **“Alpha-1 Antitrypsin deficiency”**

Alpha-1 antitrypsin, is encoded by the SERPINA1 gene, which is a member of the serpine protease inhibitor superfamily (SERPIN).The major site of production of AAT is in the liver and it sub serves as the major physiologic inhibitor of the serine protease neutrophil elastase. It also inhibits other serine proteinases including proteinase 3 (PR3) (Esnault et al,1993) and cathepsin G (Topic et al, 2009). The deficiency of AAT was first described in 1964 in two patients with emphysema.

There are many variants of the protease inhibitor (PI or SERPINA1) locus that encodes AAT -

- M allele- Most common and is associated with normal AAT levels
- S allele-Associated with slightly reduced AAT levels
- Z allele- Associated with markedly reduced AAT levels
- Null alleles- results in absence of any AAT production through a heterogeneous collection of mutations.

“Most common form of genotype of severe AAT deficiency is individuals with two Z alleles or one Z andone null allele are referred to as Pi^Z and it is found only in 1% of patients with COPD”. It has also been found that there is a significant variability in the pulmonary function

among Pi^{Z} individuals, which is explained by cigarette smoking. There is an increased likelihood of early development of COPD among Pi^{Z} individuals with cigarette smoking. Asthma and male gender also increases the susceptibility of Pi^{Z} individuals to the development of COPD.

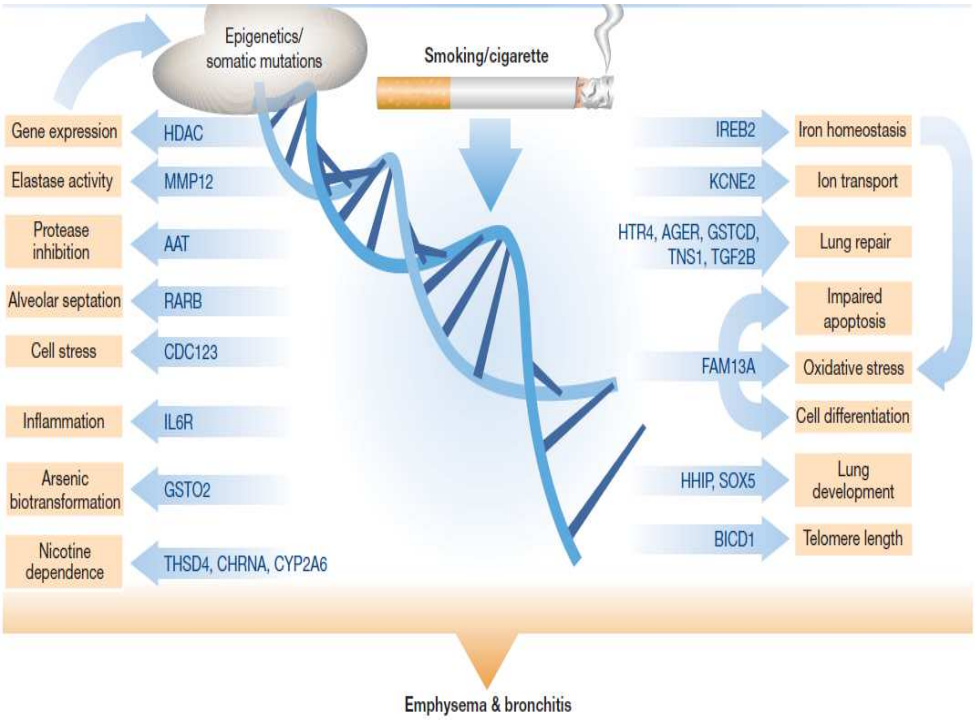
The risk of lung disease in heterozygous Pi^{MZ}individuals, those with intermediate serum levels of AAT (~60% of Pi^{MM} levels), is controversial.

It has been found in several recent large studies that Pi^{MZ} subjects are at slightly increased risk for the development of airflow obstruction, but it unclear , whether other genetic or environmental factors contributes tothis increased incidence

❖ **Other genetic risk factors**

Recent Genome wide association studies (GWAS) have identified several susceptibility loci for COPD. These include

- A region near the hedgehog interacting protein (*HHIP*) gene on chromosome4,
- A cluster of genes on chromosome 15 (including component of the nicotinic acetylcholine receptor)
- A region within a gene of unknown function (*FAM13*A regulatory SNP upstream from the *HHIP* gene



"Various newer genes involved in pathogenesis of COPD"

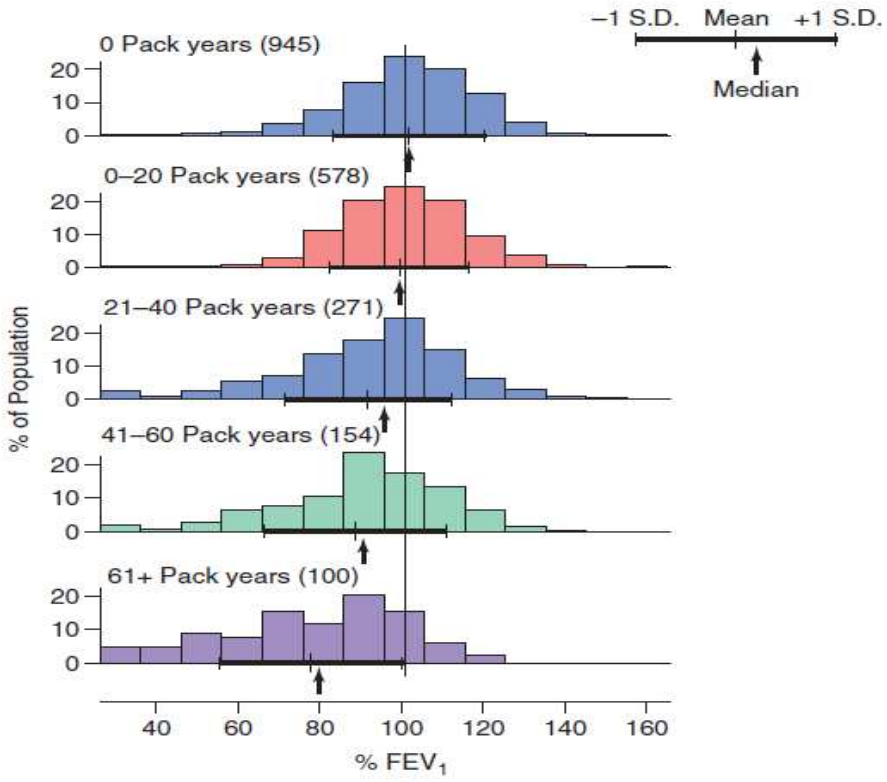
2. Airway hyperresponsiveness(AHR)

"It refers to the acute decline in maximal airflow on inhaling potential bronchoconstricting agents such as methacholine or histamine." The AHR in COPD is associated with an accelerated decline in FEV_1 and therefore considered to be a bad prognostic marker. The mechanistic features and the pathogenic role of AHR is unclear, but it has been found that smoking cessation is associated with reduction in AHR

Environmental risk factors

1. Cigarette Smoking

Cigarette smoking is found to be the major contributing factor leading to mortality from chronic bronchitis and emphysema. There is a dose-response relationship between the accelerated decline in FEV_1 and the intensity of cigarette smoking as shown by several longitudinal studies. As there is a dose-response relationship between reduced pulmonary function and cigarette smoking intensity, the prevalence of COPD increases with age. In the past there was a higher rate of smoking among male resulting in a higher disease prevalence among them, but in the present scenario, as the gender gap has diminished in smoking more disease is being reported among females.“Even though the best predictor of FEV_1 is pack years of smoking, only 15% variability in FEV_1 could be explained by no of pack years”. This suggests that environmental and genetic factors also adds to the impact of smoking in the development of airflow obstruction. Cigar and pipe smoking may also be associated with COPD, but the evidences relating to the development of disease is not so strong.



Proportional decline in FEV_1 with increase in pack years

2. Occupational exposure

The exposure to dust and fumes at work like coal mining, gold mining, and cotton textile dust, have been associated with airflow obstruction and increased respiratory symptoms. The role of dust exposure, in the absence of cigarette smoking as a risk factor for COPD is not certain.

3. Air pollution

Since some studies have reported an increased prevalence of COPD in urban areas compared to rural, the increased air pollution in urban areas has been related to this association. In some countries the

major risk factor for COPD among women is prolonged exposure to smoke produced by combustion of biomass which is used as a major source of fuel for cooking. Passive smoke exposure has been associated with a reduction in pulmonary function, the role in its development of severe airflow limitation in COPD is not certain.

4. Respiratory infections

The role of both adult and childhood respiratory infections in development and progression of COPD is yetto be proven. But infections are a major cause for exacerbation in COPD

PATHOGENESIS

- **Inflammation and extracellular matrix proteolysis**

Macrophages and epithelial cells lining the alveoli become activated, on exposure to the oxidants in cigarette smoke which lead to production of proteinases and chemokines such as matrix metalloproteinases, proinflammatory cytokins such as interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α);this leads to neutrophil recruitment. CD8+ T cells release interferon-inducible protein-10 (IP-10, CXCL7), which triggers the macrophage to produce macrophage elastase (matrix metalloproteinase-12 [MMP-12]). Matrix metalloproteinases and serine proteinases, lead to lung destruction. It has been postulated that

autoimmunity also play a role in promoting the progression of the disease as evidenced by the presence of increased B cells and lymphoid follicles in patients with advanced disease.

- **Cell Death**

Oxidant present in cigarette smoke lead to structural cell death by inhibition of mammalian target of rapamycin (mTOR), which results in cell death as well as inflammation and proteolysis. In normal lungs, macrophages uptake the apoptotic cells which results in production of growth factors which dampens inflammation,and promotes lung repair. Cigarette smoke limits repair by inhibiting the macrophage uptake of apoptotic cells.

3. Ineffective repair

Following sustaining an injury, the ability to repair the damaged alveoli by the adult lung appears limited.

SYSTEMIC INFLAMMATION IN COPD

Evidences have shown that in COPD patients with severe disease and during exacerbations, there is a high degree of systemic inflammation which results in increased levels of circulating cytokines, acute phase reactants, chemokines, and abnormalities in various circulating cell lines.[20,21] The site of origin of these systemic markers is still not certain. It can be result as a spillover from the inflammatory processes in the peripheral lung, can develop as a parallel abnormality or may be related to some of the comorbid conditions. These components of systemic inflammation may have a pathogenic role in various systemic manifestations of COPD and may also worsen the various associated comorbid diseases. It was found in a large population study that there is 2 fold to 5 fold increase in risk of cardiovascular diseases, lung cancer, pneumonia and diabetes in those with systemic inflammation as is evident from a raised level of fibrinogen, serum C-reactive protein, and leucocytes[22]. In a study conducted by using six markers of inflammation namely CRP, fibrinogen, leucocytes, TNF-α, IL-6, CXCL 8 , it was found that around 70% had evidence of inflammation and persistent inflammation was found in 16%. Persistent inflammation is associated with frequent exacerbations, increased mortality, accelerated decline in lung function.

Acute Phase proteins

❖ C- reactive protein

CRP levels are elevated in COPD patients especially during exacerbations. CRP is produced by liver in response to IL-6, therefore it may be considered as a marker of inflammation. It has been found in longitudinal studies that, FEV_1 is related to CRP levels but no association is seen with progressive decline in FEV_1[23] . Regardless of the etiology of exacerbation CRP levels are elevated in both bacterial and viral infections and the presence of persistently elevated CRP levels even after two weeks indicate the likelihood of a recurrent exacerbation.

❖ Fibrinogen

In patients with frequent exacerbations of COPD plasma fibrinogen levels have been found to be elevated[24,25]and it has been correlated to low FEV_1 and increased likelihood of hospital admission

❖ Serum amyloid A (SAA)

It is an acute phase reactant that is produced from liver as well as from inflamed tissue due to stimulation by proinflammatory cytokines. Its levels are elevated during exacerbations and the levels also correlate with the severity of exacerbations

❖ **Surfactant protein-D(SP-D)**

It is a glycoprotein and is mainly synthesized by Clara cells and type 2 pneumocytes of alveoli. It forms a part of innate immune system. Even though the levels are found to be raised in smokers and COPD patients, the correlation with severity is poor[26]. It has a poor specificity as it is elevated in other respiratory diseases like pneumonia, pulmonary fibrosis and asthma.

Cytokines.

- **Interleukin-6(IL-6)**

There is found to be a consistent elevation of IL-6 during exacerbations and it acts a stimulant for the production of circulating CRP and SAA.[27] Evidences suggest that IL-6 may have role in causing weakness of skeletal muscles.

- **Plasma TNF-α**

The plasma levels of TNF-α and its soluble receptor (sTNFR75) is seen to be increased in patients with COPD and in patients with cachexia TNF-α is also released from circulating cells. There is also found to be a correlation between TNF-α and hypoxemia[28]

- **Interleukin 1β**

An association between IL-1β and cachexia has been found in COPD patients.

- **Other cytokines**

Cytokines such as CXCL8 and other CXC chemokines play an important part in recruiting neutrophils and monocytes. CXCL 8 has been related to muscle weakness and is increased in COPD patients.

PATHOLOGY

The large airways, small airways (≤2 mm diameter), and alveoli are affected by exposure to cigarette smoke. Cough and sputum occur due to changes in large airways, while physiologic alterations are produced by changes in small airways and alveoli. Most persons with COPD have both emphysema and small airway pathology eventhough they do not appear to be related to each other mechanistically, and their relative contributions to pathogenesis vary from one person to another.

- **Large airway**

There is goblet cell metaplasia and mucus hypersecretion in large airways. The main stimuli are Neutrophil elastase, Lipopolysaccharides, IL-1β, TNF-α, cigarette smoke and oxidative stress[29]. Cigarette smoke extract have been found to act synergistically with LPS or TNF- α in the

induction of MUC5AC expression by the goblet cells which is essential for mucus production. Thus there appears to be a potential amplification of cigarette smoke and inflammatory stimuli[30]. Epithelial lining of bronchi also undergo squamous metaplasia, thus increases the risk of carcinogenesis and disrupts mucociliary clearance

- **Small airways**

The peripheral airways (i. e bronchioles <2 mm in diameter) are the major site of increased resistance to airflow in individuals with COPD[31,32]. The major pathologic lesions include increased number of inflammatory cells and structural changes, such as epithelial goblet cell metaplasia replacing surfactant secreting Clara cells, airway wall fibrosis, and smooth muscle hypertrophy[33,34,35]. The decrease in surfactant concentration may increase surface tension at the air-tissue interface, which further lead to airway narrowing or collapse. Narrowing and drop-out of small airways is the pre runner of emphysematous destruction.

- **Lung parenchyma**

There is destruction of gas-exchanging airspaces, which includes the respiratory bronchioles, alveolar ducts, and finally alveoli. The walls of small distinct air spaces become obliterated and coalescence into abnormal and much larger air spaces. In all young smokers macrophages accumulate in respiratory bronchioles and analysis of bronchoalveolar

lavage fluid reveals roughly five times as many macrophages as that from nonsmokers. Among the major pathologic types of emphysema, the most important are centriacinar and panacinar. Centriacinar emphysema, is frequently associated with cigarette smoking, which is mostprominent in the upper lobes and superior segments of lower lobes. Panacinar emphysema usually occurs in patients with AAT deficiency and it has a predilection for the lower lobes.

PATHOPHYSIOLOGY

- **Airflow obstruction**

Airflow limitation or airflow obstruction, is measured by spirometry,in patient has to perform expiratory maneuversafter inhaling to total lung capacity. Spirometry measures (FEV_1) which is the volume of air exhaled withinthe first second of the forced expiratory maneuver and forced vital capacity [FVC] defined as thetotal volume of air exhaled during the entire spirometric maneuver. Ratio of FEV_1/FVC will be reduced in patients with COPD. Unlike asthma, the reduction in FEV_1 in COPD seldom shows reversal with inhaled bronchodilators, although improvements up to 15% are common. In both normal lungs and in lungs affected by COPD, towards the end of expiration the airflow diminishes because the resistance to airflow increases as both cross-sectional area of the airways and elastic recoil of lung falls. This decrease in flow

corresponds with decreased lung volume is evident on the expiratory limb of a flow-volume curve. In the initialstages of COPD, the abnormality in airflow becomes apparent at lung volumes equal or less than the functional residual capacity which becomes visible in the flow-volume curve as a scooped-out lower part of the descending limb. The entire curve has decreased expiratory flow in more advanced stages of disease.

- **Hyper inflation**

Both “air trapping” and progressive hyperinflation are seen in advanced stage of the disease. Hyperinflation preserves the maximum expiratory airflow, because increase in lung volume leads to increase in elastic recoil pressure and this leads to decrease in airway resistance. Hyperinflation pushes the diaphragm into a flattened position which results in a number of adverse effects;

1) There is a decrease in the zone of apposition between the diaphragm and the abdominal wall, so the positive abdominal pressure created during inspiration is not applied to the chest wall. This hinders the movement of ribcage and impairs inspiration.

2) The pressure generated during inspiration are lesser than normal because of shortened muscle fibers of the flattened diaphragm as compared to that of normally curved diaphragm

3) The flattened diaphragm have an increasedradius of curvature, (r) and according to Laplace's law,

$p = 2t/r$

and to produce adequate transpulmonary pressure (p) required for tidal breathing it must generate a greater tension (t).

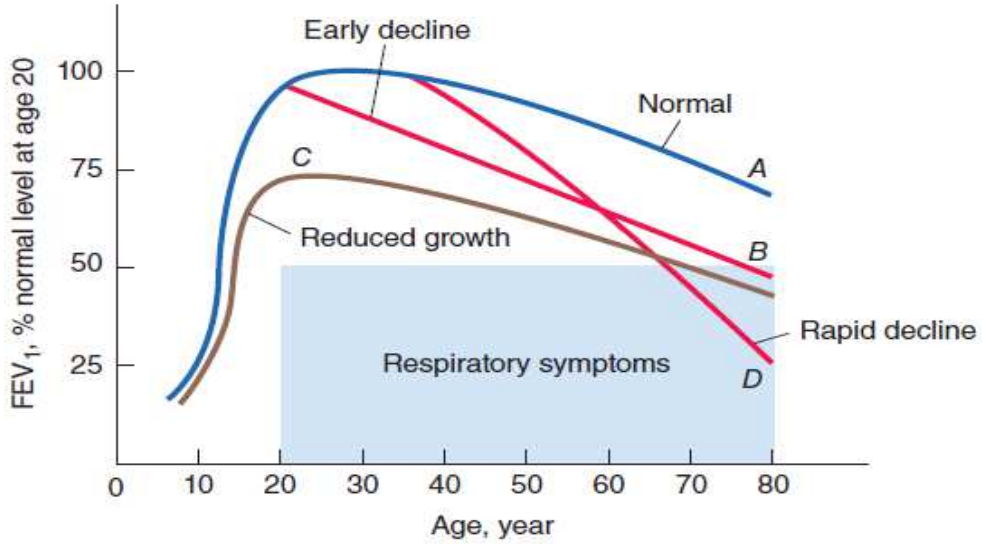
- **Gas Exchange**

Due to regional differences in compliance and resistance in airways, rates of ventilation differ in multiple parenchymal compartments. Reduction in Pao2 is mainly due to ventilation-perfusion mismatch and shuntingis minimal. So the hypoxia in COPD can be treated by modest amount of inspired oxygen and if hypoxemia is difficult to correct, then other complications should be sought for.

Natural history of COPD

The present day understanding of the natural history of COPD is from the seminal studies of Fletcher and coworkers[36]in the 1970s.The intensity of smoking exposure, exposure during growth, the baseline lung function of the individual, the timing of smoking, affect the decline in lung function. In most of the individuals pulmonary function increases with increasing age in childhood and adolescence, and declines gradually in old age. Reduced levels of FEV_1 closely correlates with mortality in COPD. This rate of decline in pulmonary function can be modified by

changing the risk factors. Cessation of smoking after marked decline in pulmonary function have not proven to be of much benefit when compared to smoking cessation atan earlier age. Genetic factors affect not only the level of pulmonary function achieved during growth but also to the rate of decline which occurs in response to smoking and exposure to other environmental factors.



"Hypothetical tracking curves of forced expiratory volume in 1s (FEV1) for individuals throughout their life spans."

"The normal pattern of growth and decline with age is shown by curve *A.* Significantly reduced FEV1 (<65% of predicted value at age 20) can develop from a normal rate of decline after a reduced pulmonary function growth phase (curve *C*), early initiation of pulmonary function

decline after normal growth (curve *B*), or accelerated decline after normal growth (curve *D*)."

Symptoms

The clinical presentation of COPD is heterogeneous. It can be asymptomatic in those with mild disease to severe wheeze, cough, and sputum production as the disease progresses. Initially dyspnea may be present only on exertion and as the disease progresses it increase in severity and patients may modify their activities to avoid becoming breathless and so they may not be aware of the actual severity of the airflow limitation. Even though the dyspnea in COPD is multifactorial a significant role is played by exercise-induced air trapping also known as "dynamic hyperinflation". Cough and sputum production in COPD is often more variable than dyspnea, and result in significant impairment of impact quality of life[37]and the cough may paradoxically increase after smoking cessation[38]. Sputum, tends to be mucoid, clear to white in appearance, and with exacerbations it becomes purulent. "Exacerbations of COPD are characterized by a sustained worsening of respiratory symptoms from the usual stable state beyond normal day to day variations"[39] .Presence of bronchiectasis is indicated by excessive sputum production (more than 2 to 3 tablespoons daily) and the prevalence of which has been reported to be between 29% and 52% in moderate to

severe COPD and it results in increased mortality[40]. Hemoptysis may be seen in both chronic bronchitis and bronchiectasis but it should also raise the concern of development of lung cancer for which COPD patients are at increased risk[41].

Physical Findings

In the early stages, no physical findings may be evident. Presence or absence of wheeze does not correlate with the severity of airflow limitation. Prolongation of expiration is more consistent finding, especially when disease progresses. FEV_1/forced vital capacity(FVC) ratio of less than 50% to 60% corresponds to a forced expiratory time of more than 6 seconds[42,43] . Signs of hyperinflation include a barrel-shaped chest, decreased breath sounds, muffled heart sounds, and increased resonance to percussion. Patients may breathe in a "tripod" position which takes advantage of the accessory muscles of the neck and upper chest and increase air movement. In severe disease patients may use pursed-lip breathing which creates back-pressure and it is also thought to reduce the dynamic hyperinflation and reduces bronchoconstriction[44]

Systemic manifestations may be present in severe disease which include features of corpulmonale, and an accentuated pulmonic component of the second heart sound. Clubbing is unlikely in COPD and if present should arise the suspicion of malignancy and other comorbidities. Two

commonly recognized clinical subtypes of COPD are “blue bloaters” and “pink puffers”. Pink puffers, are associated with significant emphysema, compensate by hyper ventilation and have muscle wasting and weight loss. Blue bloaters have chronic bronchitis and they have less ventilation and a significant ventilation perfusion mismatch than emphysema and hence appear cyanotic, develop corpulmonale and appear “bloated”.

❖ **Pulmonary Function testing and diagnosis**

1) Spirometry

Spirometry is considered as the gold standard for the diagnosis of COPD[45,46]. It plays a significant role in staging and monitoring of COPD. It helps to differentiate between respiratory diseases and other conditions that presents with similar symptoms. Spirometry as a tool for diagnosis of COPD is often underused. Epidemiological studies have thrown light into the fact that COPD will be under diagnosed in those with the disease and over diagnosed in those without the disease when spirometry is not used[47]

Components of spirometry are:

a) Forced vital capacity (FVC)

b) Forced Expiratory volume in 1 second(FEV_1)

c) FEV_1/FVC ratio

The patient is asked to perform the “Forced exhalation maneuver”, in which patient inhales maximum as possible and exhales as fast as they

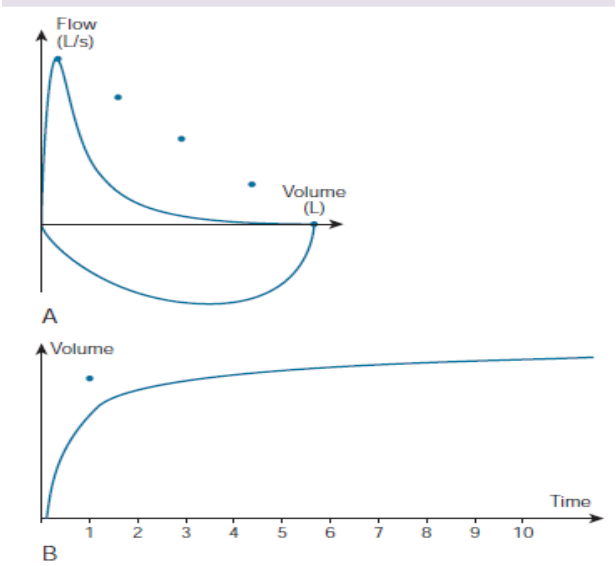
can. The amount of air the patient exhales in one breath is measured which is known as FVC and the amount of air the patient exhales in the first second is also quantified which is $FEV_{1.}$

FVC gives the measure of the amount of air the lung can hold and FEV_1 is the measure of the ease with which the air flows in the lungs. Both FVC and FEV_1 are expressed as percentage of the predicted value for the particular patient. The percent predicted is calculated based on the reference values that are calculated taking into consideration the age, gender and race of the patient. The inflammation of airways in COPD leads to narrowing which hinders the fast movement of air during expiration. This in turn leads to a decrease in FEV_1. To make a diagnosis of COPD, FEV_1 should be disproportionately decreased compared to FVC for which FEV_1/FVC ratio is calculated.

The Gold Initiative for Lung Diseases, the combined American College of Physicians, American college of chest physicians, American Thoracic society and The European Respiratory society COPD guidelines recommends a fixed cut off of FEV_1/ FVC less than .70 for making a diagnosis of COPD. To aid in easy diagnosis of COPD, this criterion has been set regardless of the age and gender. But since FEV_1/FVC declines normally with aging, setting this fixed cut-off leads to overdiagnosis of COPD in elderly[48,49] and under diagnosis in adults[50]. Another alternative is to use the Lower limit of Normal(LLN) for the cut-off of FEV_1/FVC,

which takes age, height and gender into consideration for each individual. Eventhough it minimizes age related changes in FEV_1/FVC ratio it is more difficult to perform and interpret and FEV_1/FVC ratio has a better correlation with exacerbations and mortality than LLN[51].

The advantage of spirometry is that it can beperformed in the physician's office easily and should be recommended in all patients with symptoms and risk factors suggestive of COPD.Severity of airflow obstruction is indicated by the degree of FEV_1 reduction. Along with spirometry usually a flow- volume loop is also generated in which flow is plotted on the y-axis and volume on the x-axis. The flow volume loop of COPD shows a concave appearance and a prolonged expiratory time is seen in the volume time curve.



"Fig A shows concave flow volume loop; B shows prolonged expiration" Grading of severity with spirometry

Severity of COPD graded based on FEV_1 percent predicted and it is used in GOLD and ATS/ERS recommendations. It is recommended to use post bronchodilator FEV_1 should be used to determine the stage of severity since it is more reproducible than the pre bronchodilator FEV_1[52].

"GOLD Classification of Severity of Airflow Limitation in COPD, Based on Post-Bronchodilator FEV_1"

GOLD category	**Severity**	**FEV_1 % predicted**
1	Mild	≥80%
2	Moderate	50%≤FEV_1<80%
3	Severe	30%≤FEV_1<50%
4	Very severe	<30%

Some patients may have difficulty in performing a forced exhalation maneuver due to poor mental status or coughing. The possible alternatives that have been suggested include slow vital capacity or FEV in 6 seconds (FEV6) in place of FVC and FEV_1 /FEV6 ratio instead of FEV_1/FVC ratio.[53]

2) Lung volumes

Total lung capacity (TLC) and Residual volume(RV) are measured via plethysmography in a typical pulmonary function laboratory. In

COPD, especially in emphysema TLC is increased due to lung hyperinflation as elastic recoil of lung is lost. Other lung volumes which may be increased are Residual volume (RV) and Functional residual capacity. Increase in RV is greater compared to TLC resulting in an increase in RV/TLC ratio.

3) Diffusion Capacity

Diffusing capacity for carbon monoxide (DLCO) is an indirect measure of the alveolar capillary blood volume and is decreased in the presence of emphysema, and other diseases that affect capillary bed of alveoli such as pulmonary fibrosis. If a patient has almost normal spirometry and lung volumes and severely decreased diffusing capacity and X ray imaging corresponds to emphysema, then a diagnosis of combined pulmonary fibrosis emphysema syndrome should be considered.[54]

4) Exercise testing

The 6-minute walk test(6MWT) is one of the most commonly used exercise test in COPD.6-minute walk distance (6MWD) is the distance a patient can walk in 6 minutes.[55]To perform this test, there is no need of any specialized equipment or any prior training. 6MWT helps the clinician to assess the adequacy of oxygenation during ambulation and also helps to decide regarding the need for supplemental oxygen. Patients

are also subjected to this test prior to lung transplantation to assess the functional status and to predict the prognosis. It is an indicator of mortality in COPD index and is one among the four components of BODE index. But to know the specific cause of dyspnea, a more formal cardiopulmonary exercise testing (CPET) should be performed using either a treadmill or cycle ergometer. Since most of the patients do not achieve maximal exercise capacity during the 6MWT, the result better correlates with functional exercise capacity[56]. It also correlates better with quality of life and the treatments which improve 6MWT also leads to decrease in the grades of dyspnea. CPET helps to measuremaximal oxygen uptake (_VO2), carbon dioxide output (_VCO2), maximal work rate, and anaerobic threshold. CPET is also an integral part in evaluation before a patient is subjected to lung volume reduction surgery (LVRS) because those who would benefit more from the surgery are those with a low work rate.

5) Imaging

Most commonly used imaging techniques being used in COPD are chest radiography and computed tomography(CT). Imaging is mainly used to rule out other disease with similar presentations and complications. Most commonly seen findings in Chest X-ray that may be attributed to COPD are Radiolucency, flattening of diaphragm, and in the

lateral radiograph there may be an increased retrosternal airspace in the presence of hyperinflation. Radiolucent areas may also indicate the presence of large bullae.

Chest CT is better for detection as well as quantification of the disease[57] compared to chest X-ray. It is a prerequisite for Lung volume reduction surgeries. Emphysema will be evident as low attenuation areas and bronchial thickening may also be seen. Expiratory films reveal small airway disease as well as air trapping. It also helps to rule out other respiratory diseases. Since COPD patients are also at an increased risk of lung cancer, it seems appropriate to screen individuals of age between 55 to 74 years with a smoking history of 30 pack-year including the patients who had quit smoking in the past 15 years.

4) Laboratory testing

a) Arterial blood gas analysis(ABG)

ABG is not a routine test in the evaluation of COPD patients as pulse oximetry is usually sufficient to assess the arterial blood oxygen saturation. ABGs are particularly useful in detecting hypoxemia and hypercapnia, especially during exacerbation or in individuals with severe disease. During exercise, there occurs further worsening of ABG abnormalities [58] Until the FEV_1 to ~50% of predicted there won't be any deviation of PaO_2 from normal and an increase in arterial level of carbon

dioxide (Paco2) is not usually seen unless FEV_1 is <25% of predicted and even then it may not occur. FEV1 (<25% of predicted) and chronic hypoxemia (Pao2 <55 mmHg) can lead to pulmonary hypertension which may result in cor pulmonale and right ventricular failure.

b) Erythrocytosis

Chronic hypoxemia in COPD lead to erythrocytosis and increase in hemoglobin. It also helps to differentiate from other causes of dyspnea like anemia

c) Serum bicarbonate levels

In cases of chronic hypercapnia bicarbonate levels may be elevated to compensate for the respiratory acidosis

5) Testing for $Alpha_1$ antitrypsin deficiency

According to ATS guidelines tests to detect AAT deficiency should be performed in all individuals with airflow obstruction that is persistent[59]

AAT deficiency should be suspected when;

- Emphysema occurs at a young age,
- Emphysema occurs in an individual with minimal or no smoking history,
- In presence of lower lobe predominant emphysema
- In the presence of family history of emphysema

AAT deficiency may also occur in patientswith more typical COPD. The probability of AAT deficiency is increased with serum levels below 11micromol/L (approximately 50 mg/dL when using nephelometry (i.e., immunoturbidimetry) and 80 mg/dL in case of radial immunodiffusion). In case of positive blood test the diagnosis should be confirmed by performing genotyping. Those at high-risk of developing the disease are individuals with genotypes S, Z, and null alleles are the ones with maximum deficiency). In situations where there is a discordance between serum level and genotyping, protein phenotype analysis should be performed using electrophoresis in which alleles with abnormal protein migration patterns will become evident.

6) Sputum examination

There is no indication for routine sputum evaluation in for diagnosis and further care of the COPD patients. In stable patients, there is a predominance of macrophages and few bacteria the number of which increases during acute exacerbation. Haemophilus influenzae, Streptococcus pneumonia and Moraxella catarrhalis constitute the most common pathogens which are identified on sputum culture[60] .Other organisms which occur less frequently are Pseudomonas aeruginosa, Staphylococcus aureus and other gram-negative rods. The causative role of the bacteria isolated from the sputum during acute exacerbations have

been questioned, as some longitudinal studies have shown that the probability of isolating bacteria during acute exacerbation is almost similar as that in stable state. But it has been found that isolation of bacteria from sputum during stable COPD have been associated with more number of exacerbations and increased rate of decline of lung function.

ASSESSMENT OF SYMPTOMS

❖ **Modified MRC dyspnea scale**

In the past, as COPD was considered as a disease largely characterized by breathlessness, Modified British Medical Research Council (mMRC) Questionnaire was advocated widely for symptom assessment, as it correlated well other measures of health status[61] and predicted the mortality

Grade	Degree of breathlessness related to activities
0	No breathlessness except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
3	Stops for breath after walking about 100 m or after a few minutes on level ground
4	Too breathless to leave the house, or breathless when dressing or undressing

"mMRC dyspnea scale"

risk in future. But now as more light has been thrown into the systemic nature of COPD, more comprehensive tools for symptom assessment is required.

❖ **St. George Respiratory Questionnaire**

St. George Respiratory Questionnaire[62] (SGRQ) is the most widely documented comprehensive measure and is used to measure impairment of health in both asthma and COPD patients. As it is more longer its use is mainly limited to research settings. It consists of two parts:

- Part 1(Questions 1 to 8): It produces the symptom score of the patient. It is mainly based on the patient's recollection of their symptom profile which may range from one month to one year. So it is not considered to be accurate epidemiological tool. More recently a 3- month recall version has been validated and use satisfactorily.
- Part 2(Questions 9 to 16): The activity and impact scores are derived from this part. It helps to know the current state of the patient. The Activity score gives a measure of the difficulty of the patient in carrying out activities of daily living. The Impact score addresses the psycho- social effect of the disease. Several validation studies have found that the Impact scores correlates well with respiratory symptoms. Stronger correlation was

found with breathlessness in daily life (mMRC dyspnea scale, Exercise performance(6-minute walking test) and disturbances in mood (anxiety and depression). Thus Impact score is considered to be the broadest component of SGRQ questionnaire.

A total score is produced from Part 1 and Part 2. The questionnaire has been designed for supervised self-administration. So the patients should complete the questionnaire by themselves, but clarifications of questions can be given by an appropriate trained person. Based on the responses given by the patients the scores are calculated using excel based scoring calculator. The lowest possible score is zero and maximum is 100.

- **COPD Assessment Test(CAT)**

The COPD Assessment Test is an 8 item questionnaire which gives an unidimensional measure of impairment health status in COPD[63]. The score ranges from a minimum of 0 to a maximum of 40, and it has a good correlation with SGRQ scores.

- **COPD Control Questionnaire(CCQ)**

It is self- administered 10 item questionnaire which is used to measure the extent of clinical control achieved in patients with

COPD[64,65]. The advantage of CCQ is that its short and can be performed easily. However the use of the concept of "control" in COPD has led to controversy.

Choice of cut off Points:

The CAT and CCQ scores cannot be used as a guiding tool for the purpose of initiating treatment as they do not categorise the patients into those with higher and lower symptoms. SGRQ has got a wide documentation and is the most comprehensive measure. In patients who are already diagnosed SGRQ scores less than 25 are usually not seen[66] and scores ≥ 25 are also very unlikely in healthy persons[66]. In clinical trials using long acting bronchodilator medication, it was found that the baseline weighted mean score was 44 and one standard deviation below the mean was 26[67,68] .So it has been recommended that the cut-point for starting regular treatment for symptoms is a symptom score equivalent to SGRQ score ≥ 25 which corresponds to a cut- off of 10 for CAT. CCQ equivalent scores have not yet been determined, but it appears to around 1.0- 1.5. It is difficult to keep an equivalent mMRC score as cut- off because it does not correlate well with the SGRQ score. Since mMRC is used widely a score ≥2 has been included as a cut- point for separating "less breathlessness from more breathlessness". As mMRC do not

consider symptoms other than breathlessness, it is prudent to assess other symptoms separately.

SYSTEMIC MANIFESTATIONS AND COMORBIDITIES

COPD has now been recognized as a disease which has an impact on various organ systems, the so called systemic effects and comorbidities of COPDBut it is not clear whether they are due to shared risk factors or COPD directly has a causative role.

"Observed systemic effects and comorbidities of COPD"

Systemic effects of COPD	Comorbidities of COPD
Muscle dysfunction	Cardiovascular disease
Cachexia	Lung cancer
Anemia	Osteoporosis
Muscle dysfunction	Diabetes
Autonomic dysfunction	Psychological issues: anxiety/depression
Systemic inflammation	Obstructive sleep apnea

1) Cardiovascular disease

Ischemic cardiovascular disease is undoubtedly the most leading cause of morbidity and mortality in COPD[69]. The common risk factor for this association is tobacco use but impaired lung function is postulated to act as an independent risk factor accounting for increased cardiovascular mortality even when after adjustments for smoking status. Among COPD patients FEV_1 also act as a predictor for both atherosclerosis and cardiovascular mortality. The common link between COPD and atherosclerosis is systemic inflammation. This leads to increase in acute phase reactants and elevated levels of C-reactive protein levels correlates with both presence of COPD and also presence of exacerbations, as well as severity of disease, and risk for hospitalization and death[70]. Potential (NA) mechanisms for cardiovascular disease in COPD includes:

- Systemic and lung inflammation
- Both alveolar and tissue hypoxia
- Hypercapnic acidosis
- Endothelial/ vessel wall abnormalities
- Polycythemia

2) Osteoporosis

Studies have found that the prevalence of osteoporosis in COPD patients is two to five folds more as compared age matched controls[71,72]. The shared risk factors which influence thisassociations are use of inhaled and oral steroids cigarette smoking, and a lower body mass index. But this does not explain the presence of osteoporosis in patients who are not exposed to any systemic steroids. Pulmonary rehabilitation plays a significant role in improving the functional status and by decreasing the risk of falls, might diminish the risk of fracture.

3) Diabetes

Various studies have shown that the prevalence of diabetes in COPD is between 1% and 16%[73]. Even patients with mild disease have an increased risk of developing diabetes (risk ratio- 1.5-1.8). There has been found to be an association between decreased lung function and metabolic syndrome and also with insulin resistance and increased incidence of diabetes. A study by Poulain and colleagues have shown that the presence of abdominal obesity is associated with inflammatory and metabolic abnormalities and increased development of diabetes. They found that there is an increased level of TNF-α and IL-6 which may block the signaling in insulin receptors and result in insulin resistance. This

finding further strengthens the causative role of common inflammatory pathway in the systemic effects of COPD.

4) Gastroesophageal reflux disease

COPD has been found to be associated with increased prevalence of gastroesophageal reflux disease[74] .The clinical implication of increased GERD is that it is associated with poor quality of life and frequent exacerbations[75] It has also been observed that chronic bronchitis is associated with reflux than emphysema. The clear pathogenic mechanism between this association has not been elucidated.

5) Anxiety and depression

The prevalence psychological stress (anxiety, depression) has been estimated to be around 10% and it increases as the severity increases. The major risk factors include limitation of mobility, requirement of supplemental oxygen therapy, presence of other comorbidities, and female sex[76]. The patients with anxiety experience more frequent exacerbations and risk of death is also more in patients with depression

6) Skeletal muscle dysfunction

The prevalence of muscle wasting is estimated to be around 18-36%. Inactivity appears to be the major causative factor as atrophy is more commonly found in relatively inactive muscles like quadriceps and

vastus lateralis[77]Other factors implicated in the pathogenesis are imbalance in protein synthesis and degradation, hypoxia oxidative stress, inflammation, dysfunction of mitochondria and apoptosis[78]. It has been found that quadriceps atrophy is associated with decreased exercise capacity, poor health status, increased dependence on health care resources, increased mortality that is independent of limitation of airflow.

7) Anemia

As with any other chronic, inflammatory, multisystem disease COPD is also found to be associated with anemia. Presence of anemia is an independent determinant for lower bone mineral density and elevated CRP levels as was found in the study by Rutten and colleagues. The presence of chronic inflammation also leads to resistance to erythropoietin.

8) Lung cancer

COPD is an independent risk factor for the development of lung cancer, and a patient with moderate to severe disease has almost 5- fold increased risk of lung cancer[79]. There exist an inverse correlation between risk of lung cancer and the degree of airflow limitation independent of exposure to cigarette smoke. Reduced FEV_1 is the most important risk factor for the development of lung cancer after allowing for cigarette smoke exposure as shown by cross sectional studies. The pathogenenic

mechanisms linking the two diseases appear to be multifactorial among which major role is played by inflammation and oxidative stress. NF- κB is one of proposed link between lung cancer and COPD. Nuclear factor erythroid 2- related factor 2 (Nrf2) is involved in expression of detoxifying enzymes and acts as a major defense against various carcinogens in tobacco smoke. It's down regulation is associated with increased susceptibility of COPD patients to lung cancer.

9) "Obstructive sleep apnea and obesity in COPD"

Physical inactivity has been proposed to be the risk factor for the development of obesity in COPD. Use of oral glucocorticoids also contribute to the development of truncal obesity due to the truncal redistribution of store energy. 20 % of the patients affected with OSA have been shown to have COPD in various epidemiological studies whereas independent of the severity 10% of those with COPD have OSA. The postulated mechanisms include alteration in nocturnal neuro hormonal secretion, elevated parasympathetic tone, bronchoconstriction or vasoconstriction caused by hypoxemia, stimulation of upper airway neural receptors.

BIOMARKERS IN COPD

"A biomarker is a molecule, the measurement of which reflects the disease activity". Promising biomarkers in blood that may be helpful in predicting mortality derived from large scale studies include:

1) Fibrinogen

Study by Danesh et al[80] have found that an increase in the blood level of fibrinogen by 1g/L has been associated with an increase in mortality by about 3.5 fold

2) C-Reactive protein

Several studies have shown that increase in blood levels have been associated with increased death from respiratory failure and lung cancer but it has also been shown that CRP levels have not been consistently associated with increased frequency of exacerbations

3) IL-6

It is a better predictor of three year mortality compared to IL-6 and CRP in predicting 3- year mortality. The major disadvantage is the non repeatability of IL-6 over time.

4) Bilirubin

Serum bilirubin is an emerging biomarker in COPD. Bilirubin has an antioxidant action. Horsfall et al[81]showed in their study that there

is an inverse relation between COPD mortality and bilirubin levels.

6) Pneumoproteins

Since biomarkers commonly used(CRP, fibrinogen, IL-6) are not produced in the lungs, they lack specificity. To address this problem focus has been shifted to proteins produced or modified in lungs which are referred to as pneumoproteins. SP-D and CCSP-16(Clara cell secretory protein 16) are the two major proteins which are best studied to this date. There is no relation between SP-D levels and disease progression and severity they are associated with an increased frequency of exacerbation

PROGNOSTIC FACTORS IN COPD

There are a number of factors identified as prognostic indicators for COPD. Those which are associated with accelerated decline of lung function and increased mortality include[82]

- "low FEV_1
- Airways hyper responsiveness
- History of Cigarette smoking
- Decreased body-mass index (BMI $\leq$21)
- Presence of HIV infection
- Increase in bacterial load in airways

- Decrease in exercise capacity
- Peak oxygen consumption (VO_2), measured by cardiopulmonary exercise testing
- C-reactive protein levels >3 mg/L
- Male gender
- Chest computed tomography showing presence of emphysema"

Multidimensional scales

1) BODE Index

As it has been proved that COPD is a disease that is characterized by widespread systemic inflammation affecting various organ system, there is need for novel indices which also considers the systemic nature of the disease. FEV_1aloneas used in GOLD staging is a good predictor of mortality but not of dyspnea and health status, number of exacerbations, hospitalizations[82]. In this context Celli et al(2004) developed the multidimensional BODE index which predicts not only risk of death but also the chance of hospitalization and correlates better with the health related quality of life of the patient.

Variable	Points on the BODE index			
	0	1	2	3
B—Body mass index (kg/m^2)*	>21	≤21	—	—
O—FEV_1 (% of predicted)†	≥65	50–64	36–49	≤35
D—Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
E—MMRC dyspnea scale (score)	0–1	2	3	4

The BODE Index

2) mBODE index

The modified BODE (mBODE) index makes use of an alternate dyspnea questionnaire (ie, UCSD SOBQ) and it appears to be a better predictor of mortality[83].

3) Body mass Index

Body mass index (BMI) is found to be an independent risk factor in predicting prognosis in COPD. Low body mass is associated with higher mortality[84]whereas weight gain is found to improve the prognosis

4) Fat-free mass index (FFMI)

FFMI is a better indicator of increased mortality than BMI[85]. Observational studies have shown that even though both FFMI and BMI relates well to 6- minute walk test, among the only FFMI has a better

correlation with FEV_1/FVC , the $FEV_{1,}$ ratio degree of chronic dyspnea, or the stage of disease

TREATMENT OF COPD

❖ **Stable COPD patients**

According to the available evidences, the only interventions that modify the natural course of COPD are cessation of smoking, Oxygen therapy in patients with chronic hypoxemia and lung volume reduction surgeries. Glucocorticoids may have a role in altering the mortality rate. All other treatments available mainly aim to improve the severity of symptoms, to decrease the frequency as well as morbidity associated with exacerabtions.

1) Pharmacotherapy

- **Cessation of smoking**

All COPD patients should be educated regarding the benefits of smoking cessation, and be encouraged for quitting. The pharmacological agents available include, replacement therapy for nicotine which is available as gum lozenge patch, nasal spray, and inhaler; bupropion; and varenicline, which acts as a agonist/antagonist of nicotinic acid receptor.

- **Anticholinergics**

Ipratropium and tiotropium are the two agents which are commonly used. Ipratropium being short acting produces a rapid improvements during acute exacerbations, whereas, Tiotropium being long acting, reduces exacerbations and improves symptoms. But neither of the two has any influence over the rate of decline of FEV_1.

- **Beta agonists**

Long acting Beta agonists like Formoterol and salmeterol have effects comparable to anticholinergics and has synergistic actions when compared with them.

- **Inhaled Glucocorticoids**

The effect of IGCS in reducing the mortality in COPD patients is controversial. From the available data it has been concluded that IGCS lead to 25% reduction in exacerbation frequency. So it is prudent to consider a trial of IGCS in patients with frequent exacerbations and patients with a demonstrable acute reversibility in response to IGCS.

- **Oral steroids**

It is not recommended to use chronic oral steroids because of the increased adverse events than benefits associated with them.

- **Theophylline**

In patients with moderate to severe disease its use is associated with improvement in hypoxemia and hypercapnia as well as expiratory flow rates. But monitoring of blood levels are required to decrease toxicity. The use of selective PDE-4 inhibitor Roflumilast reduces the frequency of exacerbations.

- **Antibiotics**

As bacterial infections are the major cause of exacerbations, trials administering antibiotics round the year or seasonally were conducted. But it failed to show any benefit. Recently trials have shown that daily administration of azithromycin in patients with frequent exacerbations, have reduced the frequency of exacerbations. This has been attributed to both antimicrobial and the anti-inflammatory action of azithromycin.

- **Supplemental oxygen**

It has been shown that oxygen therapy decreases mortality in patients with a resting hypoxia as evidenced by saturation less than ≤88% or <90% with evidence of right heart failure or pulmonary hypertension.

2) Non pharmacological measures.

- **Vaccinations**

All COPD patient should receive influenza vaccine annually, Polyvalent pneumococcal vaccine.

- **Pulmonary rehabilitation**

It involves educating the patient about the nature of the disease and cardiovascular condition. It has been proven that pulmonary rehabilitation leads to improvement in dyspnea, health related quality of life, increase in exercise capacity and decrease in hospital admission.

- **Lung volume reduction surgery**

The National Emphysema Treatment trial have shown that LVRS is associated with both a mortality and symptomatic benefit in the selected patients. The major indications are severe dyspnea that are not amenable to medical therapy or pulmonary rehabilitation[86], FEV_1 less than 45% of predicted, DLCO $\geq$ 20% of predicted, six-minute walk distance greater than 140 meters, post rehabilitation, Evidence of air trapping in lung volume measurements , age < 75 years. The exclusion criteria include presence of pulmonary artery systolic pressure exceeding 45 mm Hg, severe pleural disease, congestive heart failure, FEV_1< 20%, DLCO <20%, presence of diffuse disease

- **Lung transplantation**

"COPD is the second major indication for lung transplantation." According to current recommendations lung transplantation should be done in patients with severe disability even after instituting the maximal medical therapy. The patients should free from other comorbid diseases involving liver, heart and kidneys

❖ **Acute Exacerbations**

Exacerbations in COPD are defined as episodes of increased dyspnea and cough a and change in the character and amount of sputum production which may or may not be associated with fever, sorethroat or myalgia[87,88].Frequency of exacerbations correlate better with health-related quality of life than does degree of airflow limitation. The trigger for exacerbations include respiratory infections, acquisition of a new strain of bacteria in patients with chronic colonization[89], exposure to air pollulants. The goal of treatment minimize the impact of exacerbation over quality of life, decrease the decline in lung function, and prevention of subsequent exacerbations. The major indications for hospitalization include, severe underlying disease, dyspnea of higher grade or respiratory insufficiency, presence of other comorbidities, frequent exacerbations, elderly patients, and poor support at home. Treatment of exacerbations include use of :

- Bronchodilators- should be used alone or in combination with muscarinic antagonists[90].
- Corticosteroids- The recommended dose of steroids is 40- 60 mg of prednisolone per day for 2 weeks, however recent trials have shown similar benefit with 40 mg of oral prednisolone for 5 days[91]
- Antibiotics- H. influenzae, S. pneumoniae, and M. catarrhalis cause nearly 50% of the acute exacerbations.According to the guidelines it is advisable to start empirical antibiotic treatment when there is increased likelihood of infection for a duration of 5 to 10 days.
- Mechanical ventilation

• Unable to tolerate NIV or NIV failure • Respiratory or cardiac arrest • Respiratory pauses with loss of consciousness or gasping for air • Diminished consciousness, psychomotor agitation inadequately controlled by sedation • Massive aspiration • Persistent inability to remove respiratory secretions • Heart rate < 50 min^{-1} with loss of alertness • Severe hemodynamic instability without response to fluids and vasoactive drugs • Severe ventricular arrhythmias • Life-threatening hypoxemia in patients unable to tolerate NIV

“Indications for Mechanical ventilation in acute exacerbations”

MATERIALS

AND

METHODS

MATERIALS AND METHODS

SELECTION OF VOLUNTEERS

Already diagnosed stable COPD patients attending the Thoracic Medicine OPD –Rajiv Gandhi Government General Hospital from April 2025 –September 2015 are selected according to the inclusion criteria.

STUDY CENTRE

Thoracic Medicine outpatient department, Rajiv Gandhi Government General Hospital

DURATION OF STUDY

6 months

STUDY DESIGN

Observational study

SAMPLE SIZE

50 patients

INCLUSION CRITERIA

- COPD patients in stable conditions with no exacerbations due to any reason in the last 6 weeks). COPD is defined as a history of smoking and an FEV_1/FVC ratio of less than 70% , 20 minutes after salbutamol administration

EXCLUSION CRITERIA

Patients with history of:

- Inflammatory diseases (inflammatory bowel disease, rheumatologic diseases, vasculitis),
- Interstitial lung diseases, or presence of active tuberculosis
- Presence of atopy,
- Myocardial infarction in the last 6 months,
- Decompensated cardiovascular disease and
- Walking disability.

STATISTICAL METHODS

The analysis was done using statistical software SPSS 20.0.The statistical analysis within the study was done using one way ANOVA test, t test.

DATA COLLECTION AND METHODS

From COPD patients attending the Thoracic medicine department OPD, selected for clinical study as per inclusion/exclusion criteria the following data are collected: Demographic data, Past medical history. Weight, height are measured. Dyspnea severity is assigned by MMRC dyspnea scale. Patients are subjected to the six-minute walking test (6MWT), Spirometry is done. Blood is drawn for estimation of C- reactive protein. Patients are requested to fill up the vernacular version of St George respiratory disease questionnaire to assess the quality of life. Detailed clinical examination is done. BODE index is calculated from BMI, FEV1, 6- minute walking distance, MMRC dyspnea scale. FEV_1 (expressed as percentage of predicted) is used for GOLD staging. BODE index and Gold staging are correlated with CRP levels, SGRQ total score and prognostic factors.

SPONSORSHIP

No

CONFLICT OF INTEREST

None

OBSERVATION AND RESULTS

Table no 1Total number of cases

Sex	Frequency	Percent
Male	44	88.0
Female	6	12.0
Total	50	100.0

In the study group of 50 patients, 44 patients were male and 6 patients were female

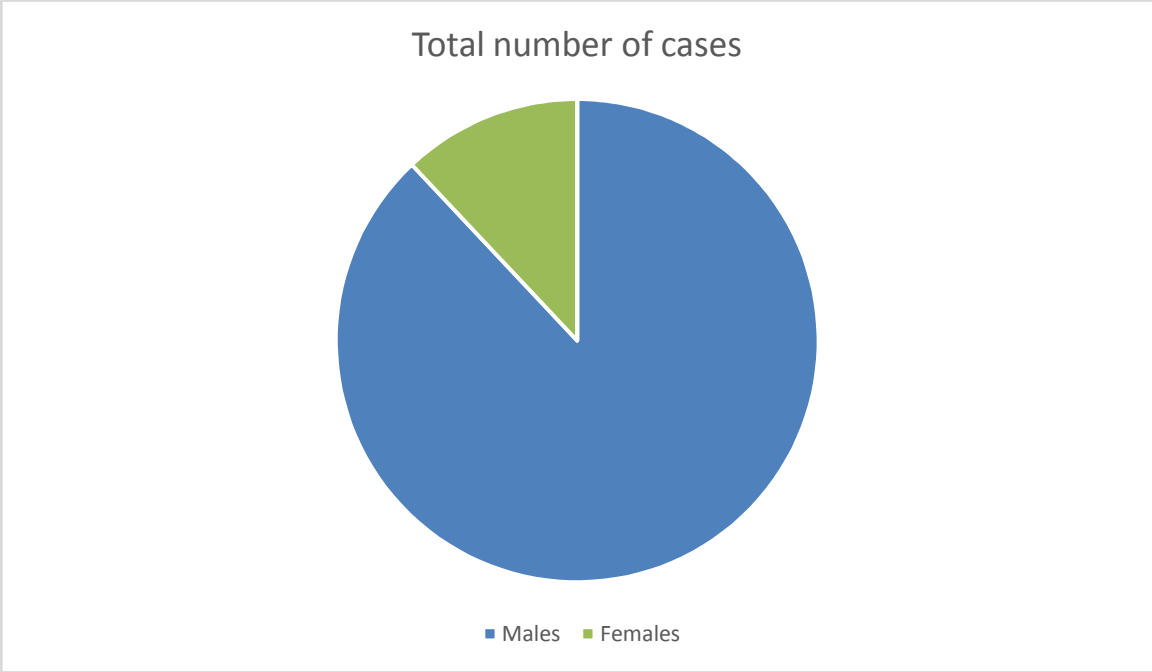


Table no: 2 Age group distribution

Age group	Total	Percentage
51-55	6	12
56-60	14	28
61-65	16	32
66-70	13	26
71-74	1	2

In the study group, the maximum incidence was in the age group of 61-65 yrs

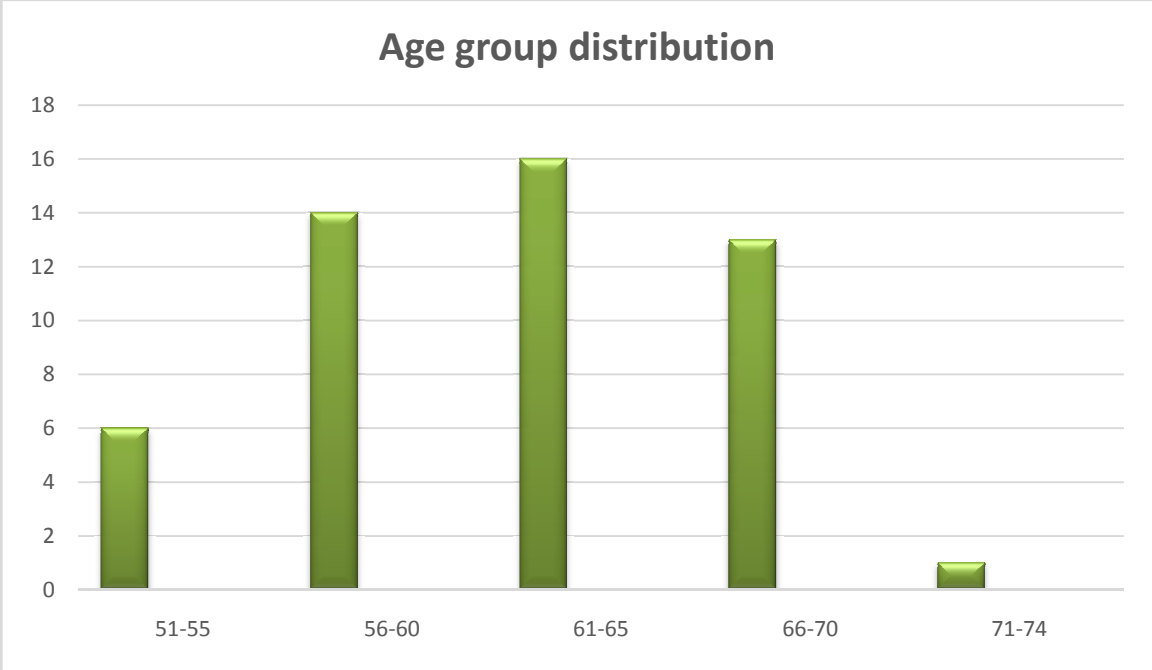


Table no: 3 Baseline demographic characteristics of the population

Variables	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	50	52	70	62.16	5.052
Pack Years	44	14	30	22.43	3.979
Duration of illness	50	3	7	4.92	1.066
No of Annual Exacerbation	50	1	6	3.40	1.143
No of Hospitalisation in previous year	50	0	5	1.88	1.043
Serum CRP Level (Mg/L)	50	4.50	26.70	14.1714	4.34393
FEV1 (L)	50	.85	1.64	1.2976	.19494
Post bronchodilator FEV1 %	50	40	71	55.53	6.409
FVC (L)	50	1.71	3.10	2.5806	.35032
Height (Cms)	50	150	170	160.90	5.136
Weight (Kgs)	50	45	65	52.70	4.156
Body Mass Index	50	18.14	30.31	20.5536	1.85211
6 Minute Walking Distance (M)	50	120	380	221.80	57.310
MMRC Dyspnoea Grade	50	1	3	2.36	.663
Bode Index Scores	50	0	8	4.82	1.711
SGRQ - Symptoms	50	32.85	95.71	68.1874	13.56043
SGRQ - Activity	50	41.73	92.51	68.5668	11.04639
SGRQ - Impact	50	20.75	91.94	63.6762	14.86575
SGRQ - Total	50	29.90	92.74	65.8348	12.62675

Analysis of Basic demographic data:

Mean age of the study group was 62.16 years with minimum of 50 years and a maximum of 70 years. Cumulative smoking pack years was 22.43 with a minimum of 14 and maximum of 30. The mean Body mass index was 20.55kg/m^2. Mean 6-MWD was 221.80 m and post bronchodilator FEV_1 % was 55.53%. The mean SGRQ scores for symptom: 68.18, activity: 68.56, impact: 63.67 and total: 65.83. the mean BODE index score was 4.82

Table no 4: Distribution of SGRQ scores according to GOLD stages

	Gold Stage	N	Mean	Std. Deviation	Std. Error Mean	P value
SGRQ - Symptoms	2	42	66.2836	13.19812	2.03651	<.05*
	3	8	78.1825	11.44631	4.04688	
SGRQ – Activity	2	42	65.5686	8.85070	1.36569	
	3	8	84.3075	7.63144	2.69812	<.001**
SGRQ - Impact	2	42	60.4983	13.46555	2.07778	
	3	8	80.3600	10.30560	3.64358	<.001**
SGRQ – Total	2	42	62.9138	11.20287	1.72864	
	3	8	81.1700	7.80972	2.76115	<.001**

In the study group, 42 patients had a GOLD stage of 2 and 8 had a GOLD stage of 3. Mean total SGRQ scores increased according to GOLD classes. There was highly significant correlation between SGRQ scores for activity impact and the total scores (p value<.001**) whereas there was still a significant correlation between SGRQ symptom score and GOLD stages(p value<.05). So SQRQ activity and impact score correlated better with GOLD stages than SGRQ symptom score.

Table no : 5 Comparison of SGRQ symptom score and BODE index

Bode index quartiles	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
					Lower Bound	Upper Bound	
0-2	5	38.5220	3.76376	1.68321	33.8487	43.1953	
3-4	14	61.2093	5.78421	1.54590	57.8696	64.5490	
5-6	25	74.5624	5.50932	1.10186	72.2883	76.8365	<.001**
7-10	6	82.6283	9.39312	3.83473	72.7709	92.4858	
Total	50	68.1874	13.56043	1.91773	64.3336	72.0412	

Table no: 5 Comparison between SGRQ activity score and BODE index

Bode index scores	N	Mean activity score	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
					Lower Bound	Upper Bound	
0-2	5	52.0440	9.43855	4.22105	40.3245	63.7635	
3-4	14	61.4971	6.19776	1.65642	57.9187	65.0756	<.001**
5-6	25	71.9212	6.38655	1.27731	69.2850	74.5574	
7-10	6	84.8550	6.42852	2.62443	78.1087	91.6013	
Total	50	68.5668	11.04639	1.56220	65.4275	71.7061	

In the study group, SGRQ symptom and activity score increases with increase in BODE index quartiles with maximum score for BODE quartile 4 and there is a highly significant correlation between the SGRQ symptom and activity score with BODE quartiles (Pvalue<.001**)

Table no: 6 Comparison between SGRQ impact scores and BODE index

Bode index quartiles	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
					Lower Bound	Upper Bound	
0-2	5	33.4380	10.63967	4.75821	20.2271	46.6489	
3-4	14	57.8214	9.86173	2.63566	52.1274	63.5154	<.001**
5-6	25	67.9280	5.56951	1.11390	65.6290	70.2270	
7-10	6	84.8200	6.01695	2.45641	78.5056	91.1344	
Total	50	63.6762	14.86575	2.10234	59.4514	67.9010	

In the study group SGRQ impact scores similar to activity and symptom score progressively increased with BODE index quartiles , with maximum SGRQ impact score for BODE index quartile 4 and two shows a highly significant correlation (pvalue<.001**)

Table no:7 Comparison between SQRQ total scores and BODE index

Bode index quartiles	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		P value
					Lower Bound	Upper Bound	
0-2	5	39.9280	8.61820	3.85417	29.2271	50.6289	
3-4	14	59.1050	5.58871	1.49365	55.8782	62.3318	
5-6	25	70.3276	3.92776	.78555	68.7063	71.9489	**< 0.001****
7-10	6	84.4067	5.91497	2.41478	78.1993	90.6140	
Total	50	65.8348	12.62675	1.78569	62.2463	69.4233	

In the study group, The SGRQ total score increases with BODE index quartiles and there is a very strong correlation is found between the two (p value<.001**)

Table no: 8 Comparison of BODE index with CRP levels

Variable		Serum CRP levels(mg/L)
Bode Index Scores	Pearson Correlation	.790(**)
	Sig. (2-tailed)	.000
	N	50
P value		<.001**

Table No :9 Comparison Gold stages with Crp levels

Gold Stage	Pearson Correlation	.447(**)
	Sig. (2-tailed)	.001
	N	50
P value	<.005**	

In the study group, on comparing CRP levels with BODE index and GOLD stages both exhibited highly significant correlation with CRP levels but GOLD staging had a weaker correlation (p value<.005**) compared BODE index.(p value<.001**)

Table no : 10 Comparison of BODE index and GOLD stages with prognostic factors

Prognostic factors		Bode Index Scores	Gold Stage
Pack Years	Pearson Correlation	.335(*)	.326(*)
	Sig. (2-tailed)	.028	.033
	N	43	43
P value		<.05*	<.05*
Duration of illness	Pearson Correlation	.731(**)	.550(**)
	Sig. (2-tailed)	.000	.000
	N	50	50
P value		<.001**	<.001**
No of Annual Exacerbation	Pearson Correlation	.685(**)	.376(**)
	Sig. (2-tailed)	.000	.007
	N	50	50
P value		<.001**	<.010*
6 Minute Walking Distance (M)	Pearson Correlation	-.823(**)	-.398(**)
	Sig. (2-tailed)	.000	.004
	N	50	50
P value		<.001**	<.005**

In the study group (table no.10) comparison was made between BODE index and GOLD stages with respect to prognostic factors.

- Both BODE index and GOLD stages had significant correlation with no pack years smoked (p value<.05) but the BODE index correlated better.
- Both BODE index and GOLD stages had highly significant correlation with the duration of illness(p value<.001**)
- With respect to the annual exacerbations, both BODE index and GOLD stages had a highly significant correlation , but BODE index exhibited a higher correlation(p value<.001**) than GOLD staging(p value<.005**)
- On comparing the relation of 6- minute walking distance with GOLD staging and BODE index, both showed a negative correlation.

The decline of 6- MWD was better correlated with increase in BODE scores (p value<.001**) than with increase in GOLD stages(p value<.005**)

Table no: 11 Comparison between SGRQ scores and post bronchodilator FEV_1

SGRQ scores		Post bronchodilator FEV1 (L)
SGRQ - Symptoms	Pearson Correlation	-.378(**)
	Sig. (2-tailed)	.007
	N	50
P value		<.01**
SGRQ - Activity	Pearson Correlation	-.415(**)
	Sig. (2-tailed)	.003
	N	50
P value		<.005**
SGRQ - Impact	Pearson Correlation	-.398(**)
	Sig. (2-tailed)	.004
	N	50
P value		<.005**
SGRQ - Total	Pearson Correlation	-.418(**)
	Sig.(2 –tailed)	.002
	N	50
P value		<.005**

In the study group it was found post bronchodilator FEV_1 had a negative correlation with SGRQ activity score, (p value< .005)), Impact score (p value< .005) total score (p value <.005), symptom score (p value<.01). Among activity, impact and symptom score, better correlation was found between FEV_1 and SGRQ activity scores.

DISCUSSION

DISCUSSION

1) In the study of M Polatlı et al[92], The mean age of the study candidates were (standard deviation; SD) 63.3 (9.3) years with 59.0% of the patients under the age of 65, and 89.9% of the participants were male. In our study the mean age was 62.16 , 88 % were males and 40 % was below 60 years.
2) In a study conducted by Kian-Chung Ong[93] the male : female ratio of incidence was 9:1 . In our study the incidence in male: female ratio is 7.3:1
3) Antonelli-Incalzi et al[94] conducted a study in which it was found that GOLD staging in COPD correlated with Health related quality of life between stages 2 and 3. In our study mostof the patients belonged to GOLD stages 2 and 3 and there was a highly significant correlation between GOLD stages and health related quality of life.
4) Sarkar SK et al[95]showed in their study that Higher BODE quartiles were associated with higher (worse) SGRQ scores .In our study also SGRQ scores increased with increase in BODE quartile and the two had a highly significant association.
5) In study conducted by Alseedi et al[96] it was found that FEV_1 correlated poorly with exacerbation frequency .In this study it is

found that even though there an association between FEV_1 and number of exacerbations, it is weaker compared to the association with BODE index quartiles.

6) The study by Nurhan Sarioglu et al[97] showed thatCRP levels have a weak but statistically significant correlation with BODE index. In this study BODE index is found to have a highly significant correlation with CRP levels.
7) In the study conducted by Marin et al[98] there was found to be a significant correlation between 6MWD and MMRC, COPD stage according to GOLD and PFT parameters. In this study also 6-MWD was found have a highly significant correlation with COPD staging according to GOLD, but compared to BODE index this association was weaker.
8) Study conducted by Funda Aksu et al[99] showed that, CRP levels are raised even in stable COPD patients independent of smoking behavior. In this study also serum CRP levels are raised and the mean value is 14.17 mg/l consistent with previous studies
9) In a study conducted by Reshu Agarwal et al[100] it was found that CRP levels correlated well with FEV_1 and hence GOLD staging. In this study also there is a highly significant correlation between GOLD stages and serum CRP levels.

CONCLUSION

CONCLUSION

In our study it was found that

- both BODE Index and GOLD staging of COPD had a highly significant correlation with health related quality of life

- Serum CRP levels were elevated in stable COPD patients and correlated with BODE index and Gold staging of COPD, but BODE index had a stronger association to CRP levels.

- BODE index had a stronger correlation with cumulative number of pack years smoked and number of annual exacerbation compared to GOLD staging.

LIMITATIONS

LIMITATION OF THE STUDY

- The number of patients included in this study was less, and it should be done involving larger number of patients

- The percentage of female patients were less in this study and it might not reflect the prevalence of COPD in females in India.

- Presence of Depression and anxiety were not assessed in this study, which are major comorbidities associated with COPD.

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ANNEXURES

ABBREVIATIONS

COPD	:	Chronic Obstructive Pulmonary Disease
FEV_1	:	Forced Expiratory Volume in the first second
FVC	:	Forced Vital Capacity
ATS	:	American Thoracic Society
ERS	:	European Respiratory Society
GOLD	:	Global Initiative for Chronic Obstructive Lung Disease
CRP	:	C- Reactive Protein
WHO	:	World Health Organisation
CDC	:	Centers for disease Control and Prevention
AAT	:	Alpha 1 Antitrypsin
AHR	:	Airway Hyperresponsiveness
SAA	:	Serum Amyloid A
SP-D	:	Surfactant protein D
LPS	:	Lipopolysaccharide
PaO2	:	Partial pressure of oxygen in blood
LLN	:	Lower Limit of Normal
RV	:	Residual Volume
TLC	:	Total lung capacity

DLCO	:	Diffusion Capacity for Carbon Monoxide
6-MWT	:	6-minute walk test
6-MWD	:	6-minute walk distance
CPET	:	Cardio Pulmonary Exercise Test
LVRS	:	Lung Volume Reduction surgery
SGRQ	:	St George Respiratory Questionnaire
CAT	:	COPD assessment test
BMI	:	Body Mass Index(kg/m^2)
mBODE	:	Modified Bode Index
FFT	:	Fat free mass index
IGCS	:	Inhaled Glucocorticoids
PDE-4	:	Phosphodiesterase-4

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

OP/ NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

MI in past six months
Active TB
History of Atopy
Rheumatological diseases
Number of annual exacerbation
Number of hospitalization

TREATMENT HISTORY :

DRUG ALLERGY :

GENERAL EXAMINATION

Pallor: Icterus: Cyanosis: Clubbing:

Lymphadenopathy: Odema:

VITALS

Pulse Rate: BP: Respiratory rate: Temperature:

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM

SPIROMETRY:

C-REACTIVE PROTEIN LEVEL:

BODE INDEX:

BODY MASS INDEX (KG/M^2) –

FEV_1(% of predicted) -

6- mt walking distance -

MMRC dyspnea grade (scale) -

ST. GEORGE RESPIRATORY QUESTIONAIRE(SGRQ) SCORE:

INFORMATION SHEET

We are conducting a study **on "COMPARISON BETWEEN BODE INDEX AND GOLD STAGING WITH RESPECT TO QUALITY OFLIFE AND C-REACTIVE PROTEIN LEVELS IN COPD PATIENTS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co- operation to undergo Pulmonary function test, 6-minute walk test and your blood sample may be valuable to us.

The purpose of this study is to investigate relationship between GOLD STAGING, BODE index and its components with serum C reactive protein levels quality of life as well as with prognostic factors like disease duration, annual exacerbation and hospital rates .

We are selecting certain cases and if you are found eligible, we would like to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature / left thumb impression of participant

Date:

Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

இதில் போடு இன்டெக்ஸ் மற்றும் கோல்டு ஸ்டேஜிங் எனப்படும் அளவுகோல்களை நெடுங்கால நுரையீரல் தொந்தரவு உள்ளவர்களிடையே (சி-ரியாக்டிவ்) புரதம்அளவு மற்றும் வாழ்க்கைத் தரத்தை ஒப்பிட்டு ஆராய்ச்சி செய்கிறோம்.

அதற்கு நுரையீரல் செயல்பாடு பரிசோதனை மற்றும் இரத்தப் பரிசோதனை அவசியம் அதற்குத் தங்கள் ஒத்துழைப்பு தேவை.

நீங்களும் இந்த ஆராய்ச்சியல் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

பங்கேற்பாளர் கையொப்பம் /
இடது கட்டைவிரல் ரேகை

தேதி :

பெயர் :

PATIENT CONSENT FORM

Study Detail	:	"COMPARISON BETWEEN BODE INDEX AND GOLD STAGING WITH RESPECT TO QUALITY OF LIFE AND C-REACTIVE PROTEIN LEVELS IN COPD PATIENTS"
Study Centre	:	Department of Thoracic Medicine, Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any ❑

data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination ,and necessary investigations.

Study investigators Patients name

name and signature Signature or thumb impression

Dr AISWARYA DHANAPALAN

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

போடு இன்டெக்ஸ் மற்றும் கோல்டு ஸ்டேஜிங் எனப்படும் அளவுகோல்களை நெடுங்கால நுரையீரல் தொந்தரவு உள்ளவர்களிடையே சி-ரியாக்டிவ் மற்றும் வாழ்க்கை தரத்தினை ஒப்பிடும் ஆராய்ச்சி.

பெயர் : தேதி

வயது : வெளிநோயாளி எண்:

பால் : அராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் சி-ரியாக்டிவ் புரதம், 6 நிமிட நடை பரிசோதனை, வாழ்க்கைத் தரம் மற்றும் நுரையீரல் செயல்பாடு பரிசோதனைகளைப் பற்றி ஆராய்ச்சியாளர் கூற அறிந்து கொண்டேன்.

மேற்கண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

நோயாளியின் பெயர்: கையொப்பம் / இடது கட்டைவிரல் ரேகை

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Aiswarya Dhanapalan
Postgraduate M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.Aiswarya Dhanapalan,

The Institutional Ethics Committee has considered your request and approved your study titled **"Comparison between GOLD staging and BODE index with respect to quality of life and C-Reactive Protein levels in COPD patients" No.30042015.**

The following members of Ethics Committee were present in the meeting held on 07.04.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.S.Baby Vasumathi, Director, Inst. Of O&G, MMC	: Member
7. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
10.Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

5/4/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MASTER CHART

S.No	NAME	AGE	SEX	PACI	DURATION OF SMOKING	NO OF ANNUAL EXACERBATION	NO OF HOSPITALISATION IN PREVIOUS YEAR	SERUM CRP LEVEL (mg/l)	FEV1(L)	FEV1 %	FVC(L)	HEIGHT (cms)	WEIGHT (kgs)	BODY MASS INDEX	6 MINUTE WALKING DISTANCE (m)	MMRC DYSPNOEA GRADE	BODE INDEX SCORES	BODE INDEX QUARTILES	GOLD STAGE	SGRQ SCORES			
																				SYMP	ACTIVITY	IMPACT	TOTAL
1	RADHAKRISHNAN	65	M	20	4	2	2	8	1.27	68	2.81	170	65	21.84	300	2	2	1	2	41.95	59.46	44.54	48.63
2	ELUMALAI	68	M	26	6	3	3	16	1.3	47	1.89	165	53	19.46	230	2	6	3	3	65.74	72.82	73.5	72
3	SENGUTHUVAN	66	M	22	4	1	1	7	1.64	61	2.42	168	65	23.8	380	1	1	1	2	32.85	41.73	28.54	33.25
4	SARANGAPANI	70	M	30	7	4	4	15	1.15	46	2.55	158	52	20.8	230	3	7	4	3	67.67	78.96	79.16	77.19
5	NATARAJAN	63	M	20	3	1	1	7.56	1.53	71	2.91	160	58	22.6	380	1	0	1	2	37.55	41.73	20.75	29.9
6	ABDUL JAFFER	66	M	20	4	3	3	4.5	1.43	59	2.83	168	59	20.9	290	2	4	2	2	67.46	53.62	55.03	56.73
7	SWAMINATHAN	64	M	18	3	3	3	10.56	1.53	64	2.75	158	53	21.23	200	2	4	2	2	51.79	57.84	64.86	60.54
8	RAJA	63	M	14	3	2	2	7.89	1.62	68	2.82	160	55	21.48	300	1	1	1	2	38.31	57.84	28.82	39.23
9	VELAYUDHAN	68	M	18	4	2	2	11.26	1.42	58	2.41	155	53	22.06	200	2	4	2	2	61.55	61.05	54.29	57.6
10	SAMIVEL	70	M	24	5	3	3	13.3	1.47	62	2.43	158	56	22.4	150	3	4	2	2	61.55	66.89	66.89	62.84
11	VETRIVEL	65	M	22	5	2	2	16.79	1.33	55	2.75	160	56	21.87	180	2	4	2	2	59.18	72.89	62.42	65.16
12	SAKUNTHALA	55	F		5	3	3	15.45	1.32	67	2	152	45	19.87	200	3	5	3	2	61.55	71.33	70.29	69.09
13	VENKATESAN	66	M	22	6	4	4	20.21	1.35	58	2.93	163	55	20.7	150	3	6	3	2	71.85	78.22	79.24	77.67
14	MANI	63	M	20	6	4	4	17.54	1.53	55	2.92	168	56	19.84	180	3	6	3	2	76.71	72.82	68.61	71.23
15	DURAIRAJ	66	M	22	7	5	5	15.38	1.36	54	2.81	163	54	20.32	150	3	6	3	3	63.95	92.51	60.46	70.92
16	KRISHNAMOORTHI	65	M	24	4	3	1	11.52	0.95	60	1.89	162	56	21.33	280	3	4	2	2	63.62	66.19	62.57	63.84
17	ELUMALAI	57	M	26	5	2	1	15.32	1.25	51	2.84	165	52	19.1	160	3	6	3	2	79.09	72.82	68.21	71.45
18	DEVATHASAN	55	M	24	3	2	1	12.24	1.31	54	2.53	158	48	19.22	260	2	4	2	2	51.79	57.84	64.86	60.54
19	KAMALA	52	F		6	3	1	26.7	0.95	46	1.82	155	46	1914	150	3	7	4	3	81.31	85.81	76.53	80.13
20	MUNUSAMY	66	M	26	5	4	2	16.32	1.33	58	2.54	160	52	30.31	200	3	6	3	2	83.2	79.67	69.73	74.98
21	RAMDOSS	58	M	18	5	3	1	7.32	1.12	53	2.71	158	54	21.63	240	2	4	2	2	56.69	60.56	70.52	65.2
22	SARAVANAN	56	M	20	5	4	1	18.33	1.23	50	2.43	162	52	19.81	180	3	6	3	2	83.2	79.67	65.43	72.72
23	MANI	68	M	22	6	3	2	14.82	1.26	56	2.61	160	50	19.53	280	3	5	3	2	75.09	66.19	61.72	65.3
24	PALANI	69	M	24	7	5	2	18.64	1.27	56	2.82	158	48	19.22	200	3	6	3	2	83.59	72.82	65.67	70.82

25	RANGAN	60	M	24	5	4	1	17.32	1.52	52	3.1	170	55	19.03	180	3	6	3	2	76.71	72.82	68.61	71.23
26	KESAVAN	55	M	30	4	3	1	12.31	1.35	51	2.6	164	52	19.33	260	2	4	2	2	63.62	51.54	55.79	55.88
27	RAJAMANI	65	M	22	4	2	0	11.56	1.55	62	2.9	166	50	18.14	280	2	4	2	2	63.83	60.35	58.23	59.8
28	VELAIYAMMAL	58	M	20	5	2	2	14.32	0.95	51	1.71	152	50	21.64	200	3	5	3	2	75.5	66.19	64.93	67.07
29	UNNAMALAI	54	M	18	6	3	1	16.52	1.42	54	2.95	165	52	19.1	220	2	5	3	2	70.45	66.19	60.2	63.72
30	DAKSHINAMOORTHY	58	M	22	5	3	1	15.21	1.53	63	2.85	160	53	20.7	220	3	6	3	2	79.09	72.82	65.67	71.83
31	GOVINDAN	63	M	20	4	3	1	10.11	1.3	51	2.8	165	58	21.3	280	1	3	2	2	70.35	53.62	41.23	49.82
32	ARUMUGAM	65	M	28	6	4	1	14.32	1.54	56	2.92	168	55	19.48	230	2	5	3	2	75.09	59.46	65.68	65.36
33	SELVI	54	F		4	3	1	10.31	1.1	56	2.1	155	53	22.06	300	2	3	2	2	54.48	66.19	36.96	48.73
34	MAHALAKSHMI	60	M		5	3	1	12.31	0.95	58	2.12	150	48	21.3	300	2	3	2	2	63.35	66.19	49.47	54.24
35	RAJAMANI	65	M	30	6	5	2	17.61	1.35	56	2.9	168	55	19.48	200	3	6	3	2	77.48	72.82	74.45	74.46
36	RAMAMOORTHY	68	M	24	4	3	1	10.23	1.45	67	2.63	158	52	20.82	250	1	2	1	2	41.95	59.46	44.54	48.63
37	GANESAN	63	M	22	5	5	2	15.87	1.27	54	2.67	160	50	19.53	180	2	5	3	2	72.66	66.19	60.08	64.02
38	MUNUSAMY	60	M	18	4	5	2	16.37	1.43	54	2.9	164	52	19.33	200	3	6	3	2	75.09	72.82	78.31	76.11
39	CHELLAN	69	M	24	6	6	3	16.92	0.9	40	2.43	160	48	18.75	140	3	7	4	3	82.38	79.67	88.63	84.56
40	ARUMUGAM	54	M	20	4	4	1	8.13	1.37	56	2.68	158	50	20.02	250	2	4	2	2	67.67	66.19	66.38	66.55
41	ELLAPPAN	64	M	24	5	4	1	7.19	1.35	58	2.63	162	52	19.81	250	2	5	3	2	75.09	66.19	64.31	66.67
42	ELUMALAI	63	M	22	5	4	1	14.53	1.29	51	2.7	164	55	20.44	230	2	5	3	2	75.09	66.19	66.85	68.02
43	MUHAMMED	58	M	20	4	3	2	17.5	1.39	57	2.67	160	53	20.7	200	2	5	3	2	70.09	66.19	66.85	67.33
44	CHANDRAN	62	M	28	5	4	2	13.26	1.28	55	2.76	162	54	20.57	220	2	5	3	2	75.09	72.82	67.12	70.17
45	KESAVAN	58	M	22	5	5	3	17.66	1.19	49	2.75	156	48	19.72	200	3	7	4	3	79.96	79.67	84.04	82
46	DEVATHASAN	55	M	16	4	4	2	16.31	1.29	53	2.8	160	53	20.7	220	2	5	3	2	70.09	72.82	64.86	68.28
47	LAKSHMI	60	F		5	4	2	17.46	0.85	50	1.89	152	45	19.47	200	3	6	3	2	77.48	72.82	80.3	77.57
48	VASANTHA	58	F		5	4	1	16.65	0.96	53	1.92	150	46	20.44	200	2	5	3	2	75.09	72.82	67.12	70.17
49	PALANISAMY	70	M	30	7	6	3	19.64	1.26	47	2.5	168	53	18.77	120	3	8	4	3	95.71	92.51	91.94	92.74
50	PANDURANGAN	65	M	24	6	3	2	21.3	1.12	47	2.73	164	50	18.59	140	3	8	4	3	88.74	92.51	88.62	89.82

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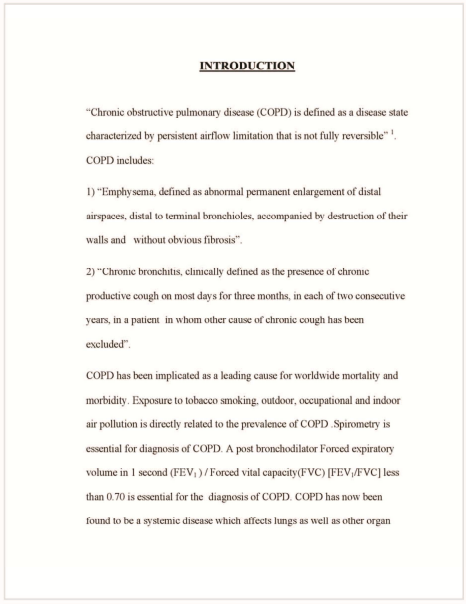

INTRODUCTION

"Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent airflow limitation that is not fully reversible" [1].
COPD includes:

1) "Emphysema, defined as abnormal permanent enlargement of distal airspaces, distal to terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis".

2) "Chronic bronchitis, clinically defined as the presence of chronic productive cough on most days for three months, in each of two consecutive years, in a patient in whom other cause of chronic cough has been excluded".

COPD has been implicated as a leading cause for worldwide mortality and morbidity. Exposure to tobacco smoking, outdoor, occupational and indoor air pollution is directly related to the prevalence of COPD .Spirometry is essential for diagnosis of COPD. A post bronchodilator Forced expiratory volume in 1 second (FEV_1) / Forced vital capacity(FVC) [FEV_1/FVC] less than 0.70 is essential for the diagnosis of COPD. COPD has now been found to be a systemic disease which affects lungs as well as other organ

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